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Title: CALCIUM INDEPENDENT PHOSPHOLIPASE A<sub>2</sub>γ  
POLYNUCLEOTIDES AND POLYPEPTIDES AND METHODS  
THEREFOR

Inventor: Richard W. Gross et al.

Docket No.: 15060-42

Gordon F. Sieckmann, Phone 314-621-5070

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FIGURE 1 (SHEET 1)

SEQ ID NO: 6

1 TGAAGCTCAGCTGATGCGAGCCCGTTGGAGTGGAACGTCATTGCCGGGAACGAGCAGTC 60  
61 GCCGTCGAGCCCTAGTGAAGTGGCGCCCTGCATCCGATTTGTTCTTCTCCCAAGGCTAC 120  
121 ATGATTACCTGAAGTTTAATAAGTAAGACCATGAATTAAGCATTTCTTAATGAAGCGT 180  
181 TCAAGAGTGAGAGAAATGTCATAGAAATAATGATTTTAAAGTATGTCTATTAACTG 240

SEQ ID NO: 1 M S I N L

241 ACTGATATATATATTACCTCCTAGTAATGCAAGAGTGTGTTGGGAAGCAGAGA 300  
T V D I Y I Y L L S N A R S V C G K Q R  
301 AGCAAGCACTGTATTCTTGTCTCACCCTAAGCATTAAGGATAAGCCACATCAGT 360  
S K Q L Y F L F S P K H Y W R I S H I S  
361 CTACAAGAGTTTTCATACAAACATATAAGATGTAATGACCAAAAGTGAAGCACAT 420  
L Q R G F H T N I I R C K W T K S E A H  
421 TCTTGAGTAAGCACTGTACTCTCCAGCAACCATGTTTACATATTGGATTGAAA 480  
S C S K H C Y S P S N H G L H I G I L K  
481 CTTAGCACTTCTGCTCCCAAGGACTTACAAAAGTGACATTTGTATGTCCTCCGATTAA 540  
L S T S A P K G L T K V N I C M S R I K  
541 AGTACTTGAAGTCTGTTCAAGGCTGTTTGGCAATCAAAATGAATGATTTTCAGCT 600  
S T L N S V S K A V F G N Q N E M I S R  
601 TTAGCTCAATTTAAGCCCAAGTCCCAATTTTAAGAAAGTATCGGATAGTGCTGTTA 660  
L A Q F K P S S Q I L R K V S D S G W L  
661 AAACAGAAAACATCAACCAAGCCATCAATCTGAAAAAATATAGTACAAATCAGCA 720  
K Q K N I K Q A I K S L K K Y S D K S A  
721 GAAAAGATCTTTCCAGAGAGAAAAGTCAATTATAGACAAAGAGAATATAGGT 780  
E K S P F P E E K S H I I D K E E D I G  
781 AAACGAGTCTTTTCATTACACAAGTCTATTAACCAAAAATTGGAGACTCATTTCTAC 840  
K R S L F H Y T S S I T T K F G D S F Y  
841 TTTTATCAATCATATTATTAATTCATAATTTCAACGTAAGGAAAAAATGCTCAACAAAAG 900  
F L S N H I N S Y F K R K E K M S Q Q K  
901 GAAATGAACATTTCCGGGACAAATCAGAACTTGAAGATAAAAAGTAGAAGAGGGAAA 960  
E N E H F R D K S E L E D K K V E E G K  
961 TTAAGATCTCAGATCTGGCATCTGGCTTATAAGCCAGGCTCAGAAATCTGTACATACG 1020  
L R S P D P G I L A Y K P G S E S V H T

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FIGURE 1 (SHEET 2)

1021 GTGACAAGCCTACAGTCCTTCTGCGATACCTGATGTTCTTCAAGTTCAACTAACA 1080  
V D K P T S P S A I P D V L Q V S T K Q  
1081 AGTATTGCTAATTTCTTCTCTGTCGCCAGGAGGTGTACAGCTTTAGTGTTAT 1140  
S I A N F L S R P T E G V Q A L V G G Y  
1141 ATTGGTGACTTGTCGCCCAATTAAAGTATGATTCAAAGAGTCAGTCAGAAGACAGAA 1200  
I G G L V P K L K Y D S K S Q S E E Q E  
1201 GAGCCTGCTAAACTGATCAGGCTGTCAAGCAAGACAGAAATGCAGAGAGAGAAAAAGCGT 1260  
E P A K T D Q A V S K D R N A E E K K R  
1261 TTATCTCTCAGCGAGAAAGATTATCGCAAGGGTGAATGATTAACAGGACCCGGCA 1320  
L S L Q R E K I I A R V S I D N R T R A  
1321 TTAGTTCAGGCATTAGAAGAACAACTGACCCCAAGCTCTGCATTACTAGGGTTGAAGAA 1380  
L V Q A L R R T T D P K L C I T R V E E  
1381 CTGACCTTTCATCTTCTAGAATTTCTGAAGGAAAGAGAGTGCGCTGCAAGGAAGAATT 1440  
L T F H L L E F P E G K G V A V K E R I  
1441 ATTCATATTTATTACGACTGAGACAAATTAAAGATGAAGAACTCTTCAGGCTGCAGTTAGA 1500  
I P Y L L R L R Q I K D E T L Q A A V R  
1501 GAAATTTGGCCCTAATTGGCTATGTGATCCAGTGAAGGAGAGAGAAATCCGAATTCTC 1560  
E I L A L I G Y V D P V K G R G I R I L  
1561 TCAATTGATGGTGAGGACACAGGGCGGTGCTCTCCAGACCCTACGAAAATTAGTT 1620  
S I D G G G T R G V V A L Q T L R K L V  
1621 GAACCTACTCAGAAGCCAGTTCATCAGCTCTTGATTACATTTGTGTTGTAAGCACAGGT 1680  
E L T Q K P V H Q L F D Y I C G V S T G  
1681 GCCATATTAGCTTTCATGTTGGGTTGTTTCATATGCCCTTGATGAATGTGAGAACTT 1740  
A I L A F M L G L F H M P L D E C E E L  
1741 TATCGAAATTAGATCAGATGATTTTCACAAAATGTCATTGTTGGAACAGTAAAAATG 1800  
Y R K L G S D V F S Q N V I V G T V K M  
1801 AGTTGAGCCATGATTTTATGACAGTCAACATGGGAAAACATTCTTAAGGATAGGATG 1860  
S W S H A F Y D S Q T W E N I L K D R M  
1861 GGATCTGCACTGATGATTGAACAAGCAAGAAACCCACATGTCTTAAGGTAGCTGCTGTA 1920  
G S A L M I E T A R N P T C P K V A A V

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1921 AGTACCATAGTAATAGAGGGATAACACCAAGCTTTGTGTTGAGAACTATGTCAT 1980  
S T I V N R G I T P K A F V F R N Y G H

FIGURE 1 (SHEET 3)

1981 TTTCCTGGAATCACTCTCATTTATTTGGAGGCTGTCAGTATAAATGTGGCAGGCCATT 2040  
F P G I N S H Y L G G C Q Y K M W Q A I  
2041 AGAGCCTCATCTGCTGCTCCAGGCTACTTTGCAGATATGCATTGGGAATGATCTTCAT 2100  
R A S S A A P G Y F A E Y A L G N D L H  
2101 CAAGATGAGGTTTGCTTCTGAATAACCCCTCGGCATTAGCTATGCATGAGTGAATGT 2160  
Q D G G L L L N N P S A L A M H E C K C  
2161 CTTGGCCAGATGTGCCGTTAGAGTGCATAGTATCCCTGGGCACCTGACGTTATGAGAGT 2220  
L W P D V P L E C I V S L G T G R Y E S  
2221 GATGTGAGAAACACGCTAACATACACAGCTTGAATACTTAACCTTCTAATGTTATCAAC 2280  
D V R N T V T Y T S L K T K L S N V I N  
2281 AGTGCTACAGATACAGAGAAGTCCATATAATGCTGATGGCCCTGTACCTCCGACACC 2340  
S A T D T E E V H I M L D G L L P P D T  
2341 TATTTAGATTCAATCCTGTATATGTGAATAACATACCTCTAGATGAAGTCGAATGAA 2400  
Y F R F N P V M C E N I P L D E S R N E  
2401 AAGCTGATCAGCTGCAGTTGGAAGGTTGAATAATACATAGAAAGAATGAACAAAAATG 2460  
K L D Q L Q L E G L K Y I E R N E Q K M  
2461 AAAAAAGTTGCAAAAATATTAGTCAGAAAAAACAACTCTGCAGAAAAATTAATGATTGG 2520  
K K V A K I L S Q E K T T L Q K I N D W  
2521 ATAAATTAATAACTGATATGTATGAAGACTTCCATTCTTTCAAAATTGTGATGAGTA 2580  
I K L K T D M Y E G L P F F S K L -  
2581 TATGCTTATGTTCTCATTAATGAAGTCTGTTTAGAAGATCAACCATTCATTAAGGAA 2640  
2641 TTGTGGGTTTCGACATGAGTTAACTTTGAATAAGTATGAATTCGAGAAATCCTGAATA 2700  
2701 AGACGCTCTCAACCAAGCTTGCAATAGCAGACAGAAATATCTTGTTACAGAAATTCATAT 2760  
2761 GGGAACTAGGCTTTAAGATGTTAATAATTAAGCTTAAGCTTAACCCCTTACTGTGCTA 2820  
2821 GTAGATTTAGTAGATATGGTGTATATGTTGATGTTGAAATATATTAATATATG 2880  
2881 TGCCGAACAAGAAACCGAAAGCTATATTTGACTGTGATTTTACTTTAGTCCCTCATAT 2940  
2941 CATGTTGAATTTATGTGATCATGATTTTATTTCAATATGGAAGAAAGCTAATTTCTTTAA 3000  
3001 ATTTACATTACCTAATATTTCTCACTAGCTATGTTCTCAATCCACACTGCCTTTTATTGT 3060

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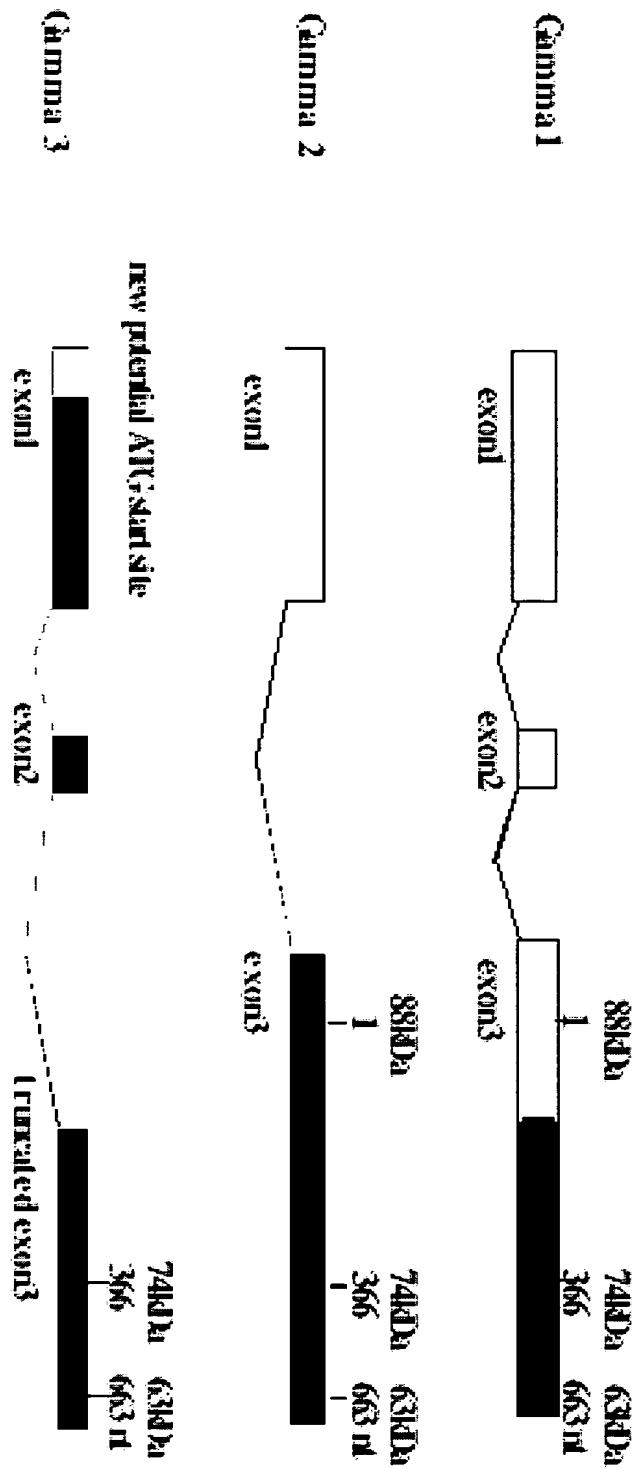
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3061 AATATCATCTAATAGATGCAGAAAATGGAATTTCTCTATTAAAGTATTTACATTTG 3120  
3121 ACATAAAAAGAACCCAGATACAGTTTCTATTTCAGATATGTTATTTTACATTGTTGG 3180  
3180 TTAATAAAGGTGAAGTTCAGTCACCACTTTTACCCCTGAAATTTCAAGATAATGCTA 3240  
3241 TATTAACTTTCCAGATCTAACACTAGCTTATCTTCCCTGTATATAAATGTTGAACT 3300  
3301 TACTGAGAGATATTCCTATCATTTACAAAAATAAATAATTAAATAATCTGTGTTAA 3360  
3361 AGGCTAATGTCATTTTAAATTAATTTTGTTCATAATGAGCTCCCTTTAGCCTTTGA 3420  
A

**FIGURE 2**

**iPLA<sub>2</sub>γ Splice Variants**



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Fig 3 Splice Variants of lPLA<sub>2</sub> $\gamma$

```
SEQ ID NO: 3 1 TGGAGCTCAGCTGATGCAAGCCCGTTGGAGTGAGCTCATTTGCCGGAACGAGCGAGTCCCGCTGCAGCCCTAGTGAC 80
SEQ ID NO: 4 2 TGGAGCTCAGCTGATGCAAGCCCGTTGGAGTGAGCTCATTTGCCGGAACGAGCGAGTCCCGCTGCAGCCCTAGTGAC
SEQ ID NO: 5 3 TGGAGCTCAGCTGATGCAAGCCCGTTGGAGTGAGCTCATTTGCCGGAACGAGCGAGTCCCGCTGCAGCCCTAGTGAC
SEQ ID NO: 2 M Q A G W S G R H C R E R A S R R C S P S D

| Exon 2

81 | Exon 3 | Exon 5 160
1 TCGCGCCCTGCATCCCGCATTTGCTTCTCTCCCAAGGCTCTACATGATTACCTGGAAGTTAATAAGTAGACCATGATTATG
2 TCGCGCCCTGCATCCCG...GTAGACCATGATTATG
3 TCGCGCCCTGCATCCCGATTTGCTTCTCTCCCAAGGCTCTACATGATTACCTGGAAGTTAATA...
C G L H P D C L L Q G L H D Y L K F N N

residues 1-32 of SEQ ID NO: 1 161
1 GCATTTCTTAAATGAAGCGTTCAAGAAGTGAGAGAATGTCATAGAAAATAATGATTTTAAAGTTATGTCTATTAATCTG M S I N L
2 GCATTNTTAAATGAAGCGTTCAAGAAGTGAGAGAATGTCATANAAAATAATGATTTTAAAGTTATGTCTATTAATCTG 140
3

141
T V D I Y I Y L L S N A R S V C G K Q R S K Q L Y F L 220
1 ACTGTAGATATATATATTTACCTCTTAGTAATGCAAGAAGTGTGTTGTTGGGAAGCAGAGAAGCAAGCAACTGTATTCTT
2 ACTGTAGATATATATATTTACCTCTTAGTAATGCAAGAAGTGTGTTGTTGGGAAGCAGAGAAGCAAGCAACTGTATTCTT
3 .....TAATGCAAGAAGTGTGTTGTTGGGAAGCAGAGAAGCAAGCAACTGTATTCTT
N A R S V C G K Q R S K Q L Y F L
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FIGURE 4 (SHEET 1)  
Full-length iPLA<sub>2</sub> $\gamma$

Primers for PCR amplification of full-length 88kDa iPLA<sub>2</sub> $\gamma$

Sense primer M444 5'-TTTGTGACATGCTCTATTATCTGACTGTAGATA-3'

Reverse primer M458 5'-GCATAGCATGCTCACAATTTGAAGAAGATGGAAGTCC-3'

SEQ ID NO: 11  
SEQ ID NO: 12

Sequence of 88kDa iPLA<sub>2</sub> $\gamma$ :

SEQ ID NO:13 atgtctattaatctgactgtagatatatatattaccctccttagtaatgcaagaagtgtt  
SEQ ID NO:1 M S I N L T V D I Y I Y L L S N A R S V  
tgtgggaagcagagaagcaagcaactgtatttcttcttctcaccctaagcattactggagg  
C G K Q R S K Q L Y F L F S P K H Y W R  
ataagccacatcagtcctacaagaagggttttcatacaacaacataaagatgtaaatggacc  
I S H I S L Q R G F H T N I I R C K W T  
aaaagtgaagcacatcttgcagtaagcactgttactctccaagcaaccatggtttacat  
K S E A H S C S K H C Y S P S N H G L H  
attggattttgaacttagcacttctgtccccaagggacttacaaaagtgaaacattgt  
I G I L K L S T S A P K G L T K V N I C  
atgtcccgtaataaagtactttgaactctgtttccaaggctgttttggcaatcaaaat  
M S R I K S T L N S V S K A V F G N Q N  
gaaatgatttcacglttagctcaatttaagccaagttcccaaatlttaagaaagtatcg  
E M I S R L A Q F K P S S Q I L R K V S  
gatagtgctgtttaaaacagaaaaaacatcaacaagccatcaaatctctgaaaaaatat  
D S G W L K Q K N I K Q A I K S L K K Y  
agtgaacaatcagcagaaaaagagtcctttccagaagagaagaaagtcacattatagacaaa  
S D K S A E K S P F P E E K S H I I D K  
gaagaagatatagtaaacgcagtccttttcatcacacaagttctataaccacaaaaattt  
E E D I G K R S L F H Y T S S I T T K F  
ggagactcattctacttttatcaaatcatatattcaataattcaaacgtaaggaaaaa  
G D S F Y F L S N H I N S Y F K R K E K  
atgtctcaacaaaaggaagaatgaacatttccgggacaaaatcagaacttgaagataaaag  
M S Q Q K E N E H F R D K S E L E D K K



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FIGURE 4 (SHEET 2)

gtagaagagggaattaaagatctccagatcctggcatcctggcttataagccaggctca  
V E E G K L R S P D P G I L A Y K P G S  
gaatctgtacatcgggtgacaagcctacaagtccttctgcatacctgatgttcttcaa  
E S V H T V D K P T S P S A I P D V L Q  
gttcaactaaacaagtatgtctaacttcttctctgcccacggaagtggtacaagct  
V S T K Q S I A N F L S R P T E G V Q A  
ttagtagtggtatatgtggtgactgtcccccaattaaagtatgttcaagaagtcag  
L V G G Y I G G L V P K L K Y D S K S Q  
tcagaagaacaggaagagcctgtctaaactgtatcaggctgttcagcaagaacagaatgca  
S E E Q E E P A K T D Q A V S K D R N A  
gaggagaataaagcgtttatctctcagcggagaataagattatcgcaaggggtgagtatgat  
E' E K K R L S L Q R E K I I A R V S I D  
aacaggccccggcattagttcaggcatgaagaagaacactgaccccaagctctgcatt  
N R T R A L V Q A L R R T T D P K L C I  
actagggtgaagaactgacttcttcatcttctaagaatttccctgaaggaaaggagtggt  
T R V E E L T F H L L E F P E G K G V A  
gtcaaggaaagaattatccatatttatacgtgagacaataaagtgatgaactctt  
V K E R I I P Y L L R L R Q I K D E T L  
caggctgcagttaggaatttggccctaattggctatgtgattccagtgaaagggaga  
Q A A V R E I L A L I G Y V D P V K G R  
ggaatccgaattctcattgatgtgtggaagaacaggggcgtgtgtctctccagacc  
G I R I L S I D G G G T R G V V A L Q T  
ctacgaaatagtgtaacttactcagaagccagttcatcagctcttgcattatcatgtt  
L R K L V E L T Q K P V H Q L F D Y I C  
ggtgtaagcacaggtgccatatagcttccatgttgggggtgttccatatagcccttgat  
G V S T G A I L A F M L G L F H M P L D  
gaaatgtgaggaacttatacgaaatagagtcagatgtatttccacaaaatgtcatgtt  
E C E E L Y R K L G S D V F S Q N V I V  
ggaacagtaaaaatgagttggagccatgcattttatgacagtcacaaacatggaacacatt

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G T V K M S W S H A F Y D S Q T W E N I  
ctaaggatagatggatctgcactgatgttgaaacagcaagaacccacatgtcct  
L K D R M G S A L M I E T A R N P T C P  
FIGURE 4 (SHEET 3)

aagtagctgtgaagtaaccatagtaaatagaggataaccaccaagctttgtgtc  
K V A A V S T I V N R G I T P K A F V F  
agaactatgtcatttccctggaatcaactcattatttggaggctgtcagtataa  
R N Y G H F P G I N S H Y L G G C Q Y K  
atgtggcaggccattagagccctcatctgtctccaggctacttgcagaatatgcatg  
M W Q A I R A S S A A P G Y F A E Y A L  
ggaaatgatcttcatcaagatggaggttcttctgaataaccctcggcattagctatg  
G N D L H Q D G G L L L N N P S A L A M  
catgagtgtaaatgtcttggccagatgtgccgttagagtgcatagtatccctgggcact  
H E C K C L W P D V P L E C I V S L G T  
ggacgttatggagtgatgtgagaacacggtaacatcacacaagcttgaaaactaactt  
G R Y E S D V R N T V T Y T S L K T K L  
tctaagtatcacacagtgctacagatcacagaagaagtcacatatatgttgatggcctg  
S N V I N S A T D T E E V H I M L D G L  
ttccctcctgcacacctattttagattcaatccctgttatgttgaaaacatcaccttagat  
L P P D T Y F R F N P V M C E N I P L D  
gaaagtcgaaatgaaaagctgcatcagctgcagttggaaggttgaatatacatagaaga  
E S R N E K L D Q L Q L E G L K Y I E R  
aatgaacaaaaaatgaaaaagttgcacaaatatattaagtcagaagaaaaaacactctgcag  
N E Q K M K K V A K I L S Q E K T T L Q  
aaaattaatgatgtgataaaatataaaactgatgatgaaggacttccattctttca  
K I N D W I K L K T D M Y E G L P F F S  
aaattgtga  
K L -

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FIGURE 5 (SHEET 1)

Sequence of 77kDa iPLA<sub>2</sub>γ  
starting at amino acid 101 (nucleotide 301)

Primers for PCR amplification of full-length 88kDa iPLA<sub>2</sub>γ

Sense primer M534 5'-TGAACGTCGACATGTCGCCGTATTAATAA-3'

SEQ ID NO: 14

Reverse primer M458 5'-GCATAGCATGCTCACCAATTTGAAAGAATGGAAGTCC-3'

SEQ ID NO: 12

SEQ ID NO: 16 atgtcccgattataaagtactttgaactctgtttccaaggctgttttgccaatcaaat  
SEQ ID NO: 15 M S R I K S T L N S V S K A V F G N Q N  
gaaatgattccacgttttagctcaatttaagccaagttcccaaatttaagaaaagtatcg  
E M I S R L A Q F K P S S Q I L R K V S  
gtagtggctggttaaaacagaaaacatccaacaagccatcaaatctctgaaaaaatat  
D S G W L K Q K N I K Q A I K S L K K Y  
agtgaacaatcagcagaaaagagtcctttccagaagagaagaaagtcacattatagacaaa  
S D K S A E K S P F P E E K S H I I D K  
gaagaagatatagtaaacgcagtccttttccattacacaaagttctataaccacaaaattt  
E E D I G K R S L F H Y T S S I T T K F  
ggagactcattctacttttatacaaatcatattcatattccaacgtaaggaaaaa  
G D S F Y F L S N H I N S Y F K R K E K  
atgtctcaacaaaagaaaatgaacattccgggacaacatcagaacttgaagataaaaag  
M S Q Q K E N E H F R D K S E L E D K K  
gtagaagagggaattaaagatctccagatccctgcatccctggttataagccagggtca  
V E E G K L R S P D P G I L A Y K P G S  
gaatctgtacatacgttggaacaagcctacaagtccttctgcgatatcctgatgttcttcaa  
E S V H T V D K P T S P S A I P D V L Q  
gtttcaactaaacaaagtattgtctaactttcttctcgtcccaagggaagtgtaagaagct  
V S T K Q S I A N F L S R P T E G V Q A

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FIGURE 5 (SHEET 2)

ttagtagtgggttatattgtgtgacttgtccccaattaaagtattccaagagtcag  
L V G G Y I G G L V P K L K Y D S K S Q  
tcagaagaacaggaagagcctgtctaaactgatacaggctgtcagcaagaacagaatgca  
S E E Q E E P A K T D Q A V S K D R N A  
gaggaagaaaaagcgttatctcttcagcaggaagaaagtattatcgcaagggtgagtattgat  
E E K K R L S L Q R E K I I A R V S I D  
aacaggaacccgggcattagttcagggcattaagaagaacaactgaccccaagctctgcatt  
N R T R A L V Q A L R R T T D P K L C I  
actagggttgaagaactgactcttctcattcttagaatttctcctgaaggaaaaagagtgct  
T R V E E L T F H L L E F P E G K G V A  
gtcaaggaaagaattatcccatatttattacgactgagacaataatgaagatgaactctt  
V K E R I I P Y L L R L R Q I K D E T L  
caggtcgcagttagaagaatttggccctaatttggtctatgtgacccagtgaaaggagaga  
Q A A V R E I L A L I G Y V D P V K G R  
ggaatccgaattctctcaattgatgtggaagaagggcggtgtgtctctccagacc  
G I R I L S I D G G T R G V V A L Q T  
ctacgaaaattagttgaacttactcagaagccagttcatcagctcttggattacatttgt  
L R K L V E L T Q K P V H Q L F D Y I C  
ggtgtaagcacaggtgccaatatagcttccattgttggtgtttcatatgccccttgat  
G V S T G A I L A F M L G L F H M P L D  
gaaatgtgaagaactttatcgaaaattaggtatcagatgtatttccacaaaatgtcatgtt  
E C E E L Y R K L G S D V F S Q N V I V  
ggaacagtaaaaatgagttgagggccatgcatctttatgacagtcacaacatgggaaaaacatt  
G T V K M S W S H A F Y D S Q T W E N I  
cttaaggatagatggatctgcactgcatgatgtgaacacagcaagaagaaacccacatgtcct  
L K D R M G S A L M I E T A R N P T C P  
aaggtagctgtgttaagtaacatagtaaatagagggataacaccccaagcttltgtgttc

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K V A A V S T I V N R G I T P K A F V F

FIGURE 5 (SHEET 3)

agaactatggtcatttctctggaatcaactctcatttggaggctgcagtataaa  
R N Y G H F P G I N S H Y L G G C Q Y K  
atgtggcaggccattagagccctcatctgtgtctccaggctacttgcagaatatgcatg  
M W Q A I R A S S A A P G Y F A E Y A L  
ggaatgatcttcacatcaagatggagggttcttctgaataacccttcggcattagctatg  
G N D L H Q D G G L L L N N P S A L A M  
catgagtgttaaatgtctcttgccagatgtgccgttagagtgcatagtatccctgggcaact  
H E C K C L W P D V P L E C I V S L G T  
ggacgttatgagtgatgtgagaacacggttaacatcacacaagcttgaaaactaact  
G R Y E S D V R N T V T Y T S L K T K L  
tctaattgtatcaacagtgctacagatcacagaagaagttccatataatgttgatggcctg  
S N V I N S A T D T E E V H I M L D G L  
ttacctcctgacacctatttagattcaatcctgttaattgtgaaaacatacctctagat  
L P P D T Y F R F N P V M C E N I P L D  
gaaagtcgaaatgaaagctggtcagctgcagttggaagggttgaatatacatagaaga  
E S R N E K L D Q L Q L E G L K Y I E R  
aatgaacaaaaaatgaaaaagttgcaaaaatatattagtcagaaaaaaacactctgcag  
N E Q K M K K V A K I L S Q E K T T L Q  
aaaattaatgattgataaaataaaaactgatatgtatgaaggacttccattctttca  
K I N D W I K L K T D M Y E G L P F F S  
aaattgtga  
K L -

FIGURE 6 (SHEET 1)

Sequence of 74kDa iPLA<sub>2</sub>γ  
starting at amino acid 122 (nucleotide 364)

Primers for PCR amplification of full-length 88kDa iPLA<sub>2</sub>γ

Sense primer M533 5'-TCAAGTCGACATGATTTCACGTTAGC-3'

SEQ ID NO: 17

Reverse primer M458 5'-GCATAGCATGCTCACAAATTTGAAGAAGATGGAAGTCC-3'

SEQ ID NO: 12

SEQ ID NO: 19 atgattcacgttttagctcaatttaagccaagttcccaaatTTtaagaaaagtatcg  
SEQ ID NO: 18 M I S R L A Q F K P S S Q I L R K V S  
gatagtggctggttaaaacagaaaaaacatcaaacaggccatcaaatctctgaaaaatat  
D S G W L K Q K N I K Q A I K S L K K Y  
agtgaacaatcagcagaaaagagtcctttccagaagagaaaagtcacattatagacaaa  
S D K S A E K S P F P E E K S H I I D K  
gaagaagatatagtaaacgcagtccttttccattacacaagttctataaccacaaattt  
E E D I G K R S L F H Y T S S I T T K F  
ggagactcattctacttttatccaatcatatattcatatttcaaacgtaagaaaaa  
G D S F Y F L S N H I N S Y F K R K E K  
atgtctcaacaagaagaatgaacatttccgggacaaatcagaacttgaagataaaaag  
M S Q Q K E N E H F R D K S E L E D K K  
gtagaagaggggaattaaagatctccagatccctgcacccctgcttataagccaggtca  
V E E G K L R S P D P G I L A Y K P G S  
gaatctgtacatacgytgacaagccctacaagtccttctgcgatacctgatgttctcaa  
E S V H T V D K P T S P S A I P D V L Q  
gttccaactaaacaagatattgctaacttcttctctcgccccacgggaagtggtacaagct  
V S T K Q S I A N F L S R P T E G V Q A  
ttagttagtggttatattgttgactgtgtcccaaattaagtatgatccaagagtcag  
L V G G Y I G G L V P K L K Y D S K S Q  
tcagaagaacaggaagagcctgcttaaaactgatcaggctgtcagcaagaagacagaatatgca

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FIGURE 6 (SHEET 2)

aacaggaccgggcatagttcaggcattaaagaacaactgacccaagctctgcatt  
N R T R A L V Q A L R R T T D P K L C I  
actagggtgaagaactgacttttcattccttctagaatttcctgaaggaaaggagtgct  
T R V E E L T F H L L E F P E G K G V A  
gtcaaggaaagaattattccattatttaccagctgagacaattaaagatgaactctt  
V K E R I I P Y L L R L R Q I K D E T L  
caggctgcagttgagaattttggccctaatgtgtatgtgcatccagtgaaaggaga  
Q A A V R E I L A L I G Y V D P V K G R  
ggaatccgaattctctcaattgatgtgtggaagacaaggggcggtgtctctccagacc  
G I R I L S I D G G T R G V V A L Q T  
ctacgaaaattagttgaacttaccagaagccagttcaccagctcttgattacattgt  
L R K L V E L T Q K P V H Q L F D Y I C  
ggtgtaagcacagtgccatatagctttcattgtgtgtgtttccatatgcccctggat  
G V S T G A I L A F M L G L F H M P L D  
gatgtgaggaactttatcgaattaggtatcagatgtattttcacaaaatgtcattgt  
E C E E L Y R K L G S D V F S Q N V I V  
ggaacagtaaaaatgagttgagccatgcattttatgacagtcacaacatggygaacat  
G T V K M S W S H A F Y D S Q T W E N I  
cttaaggatagtggtgctgtcactgatgtatgaacacagcaagaacccccacatgtcct  
L K D R M G S A L M I E T A R N P T C P  
aagtagctgtgtaagtaaccatagtaaatagaggataacacccaagctttgtgttc  
K V A A V S T I V N R G I T P K A F V F  
agaaactatgttcatttccctggaatcaactctcattatttggaggctgtcagataaa  
R N Y G H F P G I N S H Y L G G C Q Y K  
atgtggcaggccattagagcctcctgtctgtcctcaggctactttgcagaatatgcatg  
M W Q A I R A S S A A P G Y F A E Y A L  
ggaatgatcttcatcaagatgaggtttgtcttgaataaaccttcggcatagctatg  
G N D L H Q D G G L L L N N P S A L A M  
catgagtgtaaatgtcttggccagatgtgcccgttagagtgcatagtatccctgggcaat  
H E C K C L W P D V P L E C I V S L G T  
ggacgttatgagagtgatgtgagaacacggttaacatacacaagcttgaaaactaaact  
G R Y E S D V R N T V T Y T S L K T K L  
tctaattgtatcaacagtgctacagatacagaagaagttccatatatatgtgtgtgcctg

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**FIGURE 6 (SHEET 3)**

S N V I N S A T D T E E V H I M L D G L  
 ttacctcctgcacacctattttagatccaatcctgtaatgtgtgaaacacatacccttagat  
 L P P D T Y F R F N P V M C E N I P L D  
 gaagtcggaatgaaaaagctggtcagctgcagtttggaaggttgaatatacatagaaga  
 E S R N E K L D Q L Q L E G L K Y I E R  
 aatgaacaaaaaatgaaaaaagttgcaaaaatatlaagtcagaagaaaaaacactctgcag  
 N E Q K M K K V A K I L S Q E K T T L Q  
 aaaatlaatgattgataaataaataaacctgatattgtatgaaggacttccattctttca  
 K I N D W I K L K T D M Y E G L P F F S  
 aaattgtga  
 K L -



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FIGURE 7 (SHEET 1)

Sequence of 63kDa iPLA<sub>2</sub>γ  
starting at amino acid 221 (nucleotide 661)

Primers for PCR amplification of full-length 88kDa iPLA<sub>2</sub>γ

Sense primer M530 5'-GTAAGTCGACCAATGCTCAACAAAAAGG-3'

SEQ ID NO: 20

Reverse primer M458 5'-GCATAGCATGCTCACCAATTGTGAAAAGAATGGAAGTCC-3'

SEQ ID NO: 12

SEQ ID NO: 22 atgtctcaacaaaaggaaaatgaacatttccgggacaatcagaacttgaagataaaag  
SEQ ID NO: 21 M S Q Q K E N E H F R D K S E L E D K K  
gtagaagaggggaattagatctccagatccctggcatccctgttataagccaggctca  
V E E G K L R S P D P G I L A Y K P G S  
gaatctgtacatagcgtggacaagcctacaagtccttctgcgatacctgatgttcttcaa  
E S V H T V D K P T S P S A I P D V L Q  
gttccaactaaacaagtattgtctaactttcttctcgtccacggaaggtgtacaagct  
V S T K Q S I A N F L S R P T E G V Q A  
ttagtagtggttatatgtgtgactgtgtccccaattaaagtattcacaagaagtcag  
L V G G Y I G G L V P K L K Y D S K S Q  
tcagaagaacaggaagagcctgtctaaactgtatcagcgtgtcagcaagaacagcaaatgca  
S E E Q E E P A K T D Q A V S K D R N A  
gaggagaaaaagcgtttatctcttcagcgagaaaagattatcgcaaggtgagttatgat  
E E K K R L S L Q R E K I I A R V S I D  
aacaggacccgggcattagttcaggcattagaagaacaacactgacccaagctctgcatt  
N R T R A L V Q A L R R T T D P K L C I  
actagggttgaagaactgacttttcatcttctagaatttctgaagaaaggagtgct  
T R V E E L T F H L L E F P E G K G V A  
gtcaaggaagaattatcccatatttatacgaactgagacaataaagatgaactctt  
V K E R I I P Y L L R L R Q I K D E T L  
caggctgcagttagagaattttggccctaattggctatgtggtccagtgaaagggaga

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Q A A V R E I L A L I G Y V D P V K G R  
FIGURE 7 (SHEET 2)

ggaatccgaattctctcaattgatgtgtgagggaacaaggcggtgtgtctctccagacc  
G I R I L S I D G G T R G V V A L Q T  
ctacgaaaattagtgaacttactcagaagccaggttcacagctcttgattacattgt  
L R K L V E L T Q K P V H Q L F D Y I C  
ggtgtaagcacaggtgccatattagcttcatgttgggtgttccatatgccccttgat  
G V S T G A I L A F M L G L F H M P L D  
/ gaatgtgaggaaactttatcgaaaattaggatcagatgtatttcacaaaatgtcattgt  
E C E E L Y R K L G S D V F S Q N V I V  
ggaacagtaaaaatgagttggagccatgcattttatgacagtcacaacatgggaaaacatt  
G T V K M S W S H A F Y D S Q T W E N I  
ctaaggataggatgggctctgcactgatgtgaacacagcaagaaacccccacatgtcct  
L K D R M G S A L M I E T A R N P T C P  
aaggtagctgtgtaagtaaccatagtaaatagaggataacacccaagcttctgtctc  
K V A A V S T I V N R G I T P K A F V F  
agaacctatgtcatttcccttggaatcaactctcatatttgggaggctgtcagtataa  
R N Y G H F P G I N S H Y L G G C Q Y K  
/ atgtggcaggccattagagcctcatctgtctgtccaggctacttgcagatatgcattg  
M W Q A I R A S S A A P G Y F A E Y A L  
ggaatgatcttcacatcaagatggagttgtctctgaataacccttcggcatagctatg  
G N D L H Q D G G L L L N N P S A L A M  
catgagtgaatgtcttggccagatgtgcccgttagagtgcatagtatccctgggcact  
H E C K C L W P D V P L E C I V S L G T  
ggacgttatgagagtgatgtgagaacaacaggtacacacaacagcttgaaaactaact  
G R Y E S D V R N T V T Y T S L K T K L  
tctaattgtatacaacagtgctacagatacagaagaagttccatataatgttgatggcctg  
S N V I N S A T D T E E V H I M L D G L  
ttacctcctgcacacctatttagattcaatccctgtaattgtgtgaaaacatacctctagat

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L P P D T Y F R F N P V M C E N I P L D

FIGURE 7 (SHEET 3)

gaaagtcgaaatgaaaagctggatcagctgcagttggaagggttgaatacatagaaga  
E S R N E K L D Q L Q L E G L K Y I E R  
aatgaacaaaaaatgaaaagctggcaaaatatagtcagaagaaaaaacactctgcag  
N E Q K M K K V A K I L S Q E K T T L Q  
aaaatgaatggatgataaaatlaaaactgatatgtgaaggacttccattcttcca  
K I N D W I K L K T D M Y E G L P F F S  
aaatgtga  
K L -

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FIGURE 8



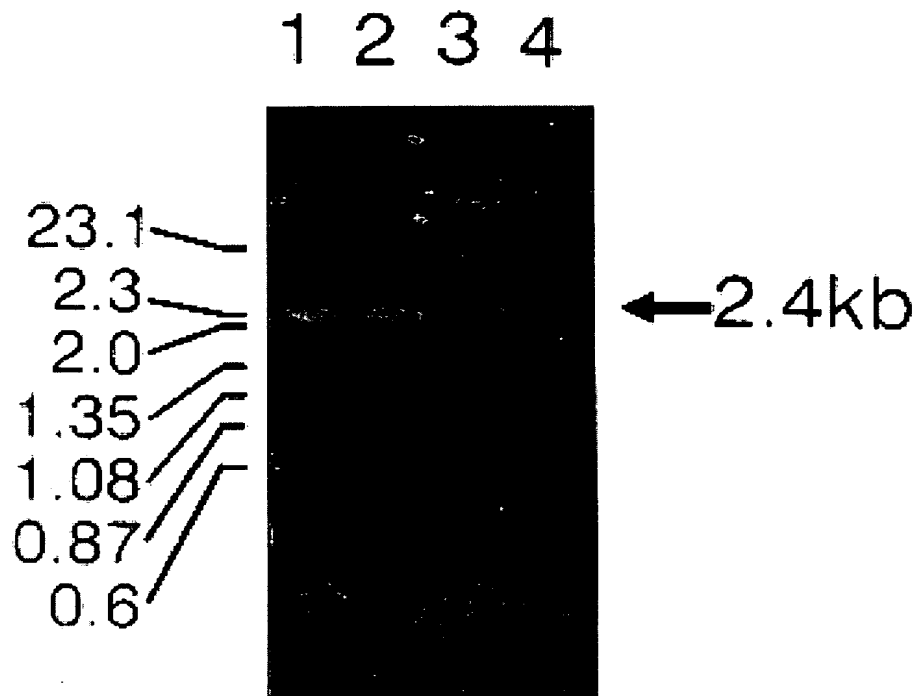
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**FIGURE 9**

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# FIGURE 10

## Potential Alternative Exon 5 Splice Variant of Human iPLA<sub>2</sub>γ

### A. Reported Splice Sequence (gc/ag)

<u>Exon 5 (SEQ ID NOS 43-44)</u>	<u>Intron 5</u>	<u>Exon 6 (SEQ ID NOS 45-46)</u>	<u>Source</u>
...CAG CGA GAA AAG	gcaagt...ttgtag	ATT ATC GCA AGG GTG AGT	(Tanaka et al)
Q R E K		I I A R V S	BBRC 272: 320, 2000

### B. Potential Splice Variant (gt/ag)

<u>Exon 5 (SEQ ID NOS 47-48)</u>	<u>Intron 5</u>	<u>Exon 6</u>	<u>Source</u>
..GAA AAG GCA AGT TGT TCA GT	gtgctt..tcgcaag	G GTG AGT	(Gross lab)
E K A S C S V		V S	JBC 275: 9937, 2000

The incidence of gc/ag splice variants like the one shown in "A" is 0.56%. The variant "A" has been reported in the literature, reported in GenBank, and cloned in our lab.

The splice variant gt/ag occurs with a frequency of 98.71% among genes. However, variant "B" iPLA<sub>2</sub>γ sequence has not been cloned.

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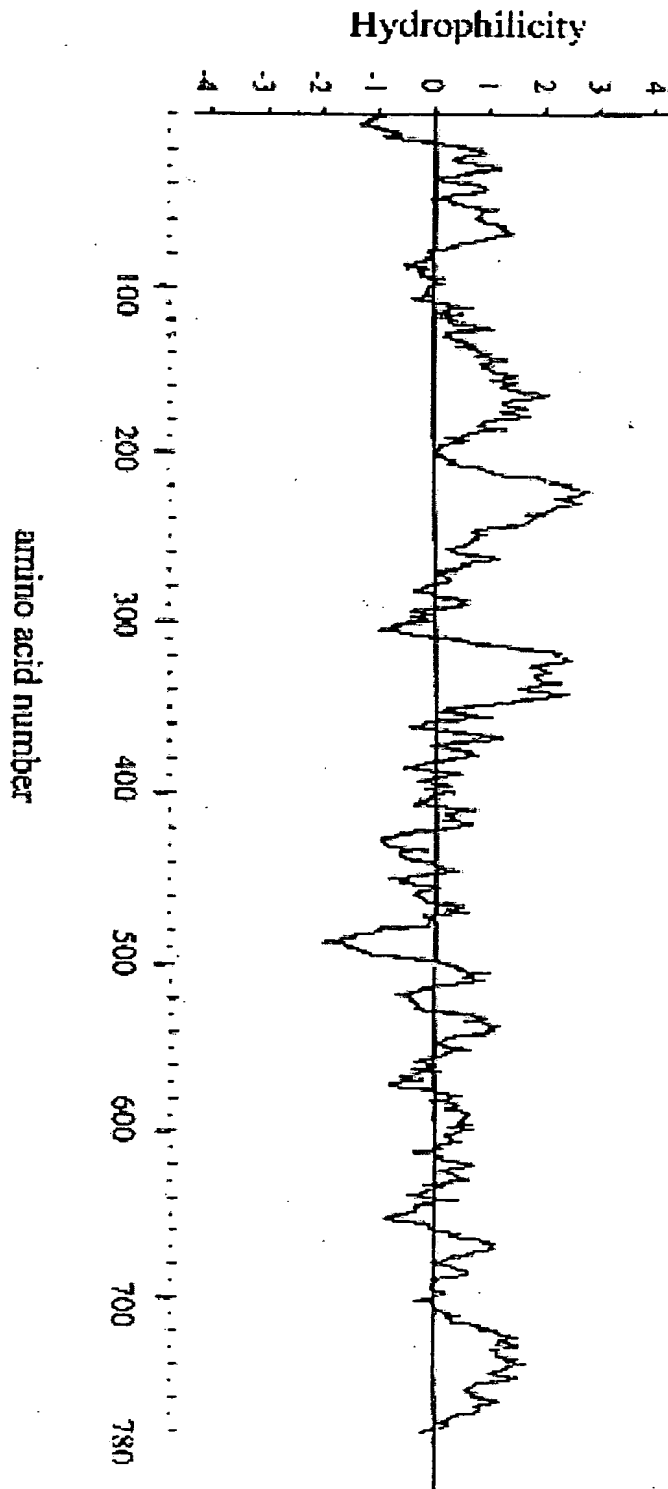
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FIGURE 11



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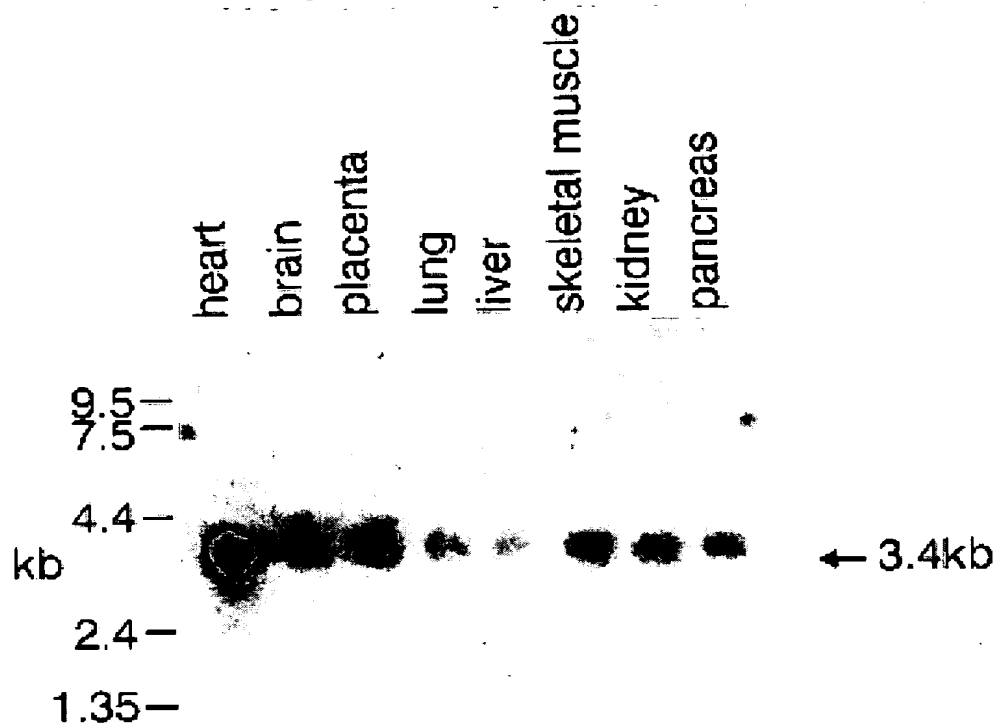


FIGURE 12



Title: CALCIUM INDEPENDENT PHOSPHOLIPASE A<sub>2</sub>γ  
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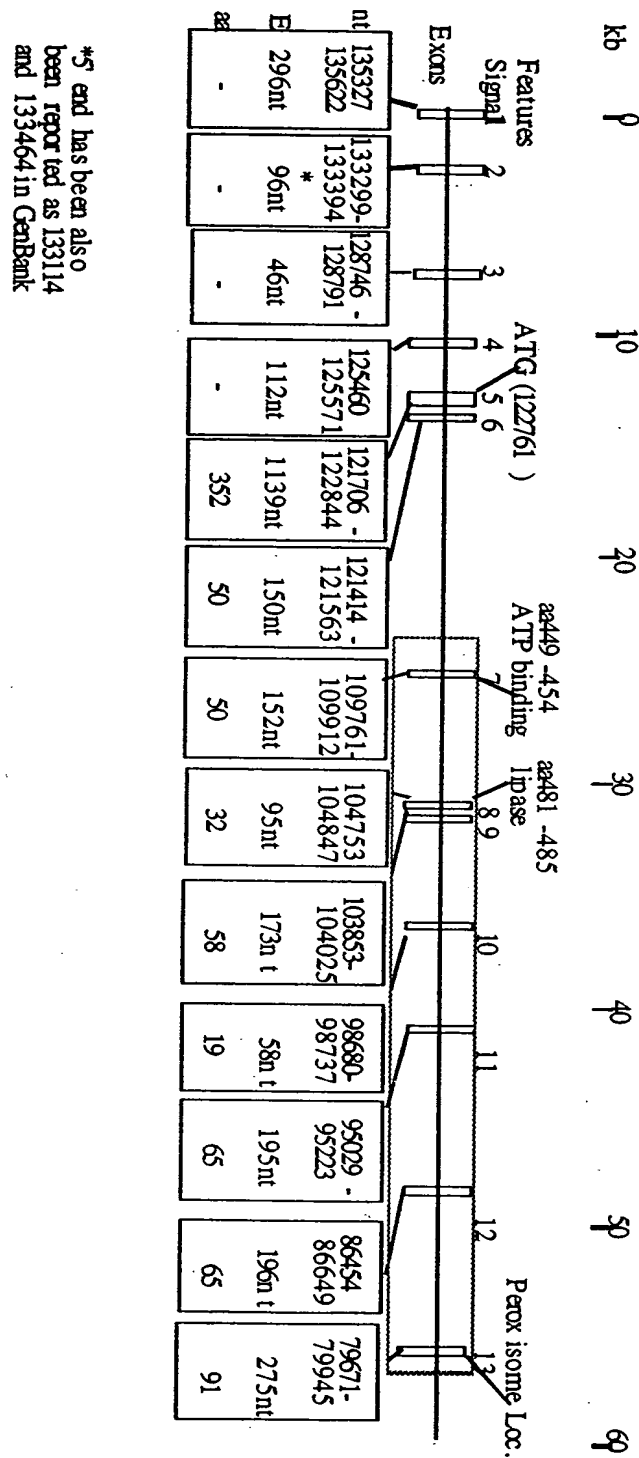
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FIGURE 13



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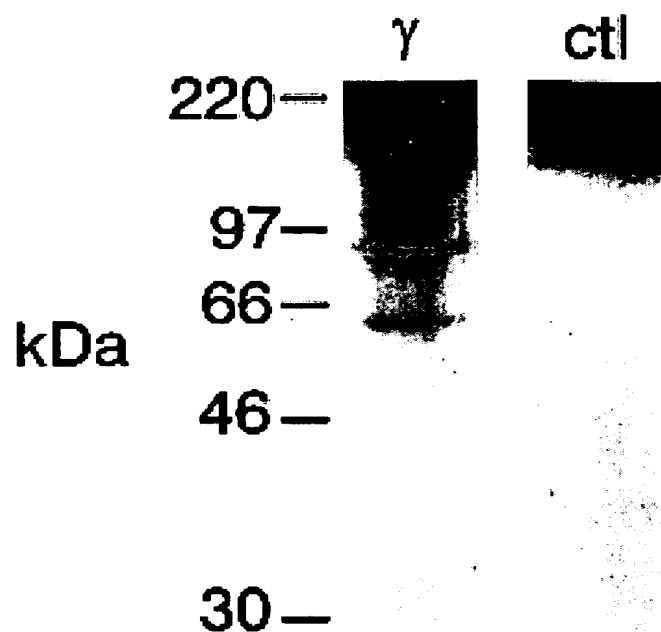


FIGURE 14

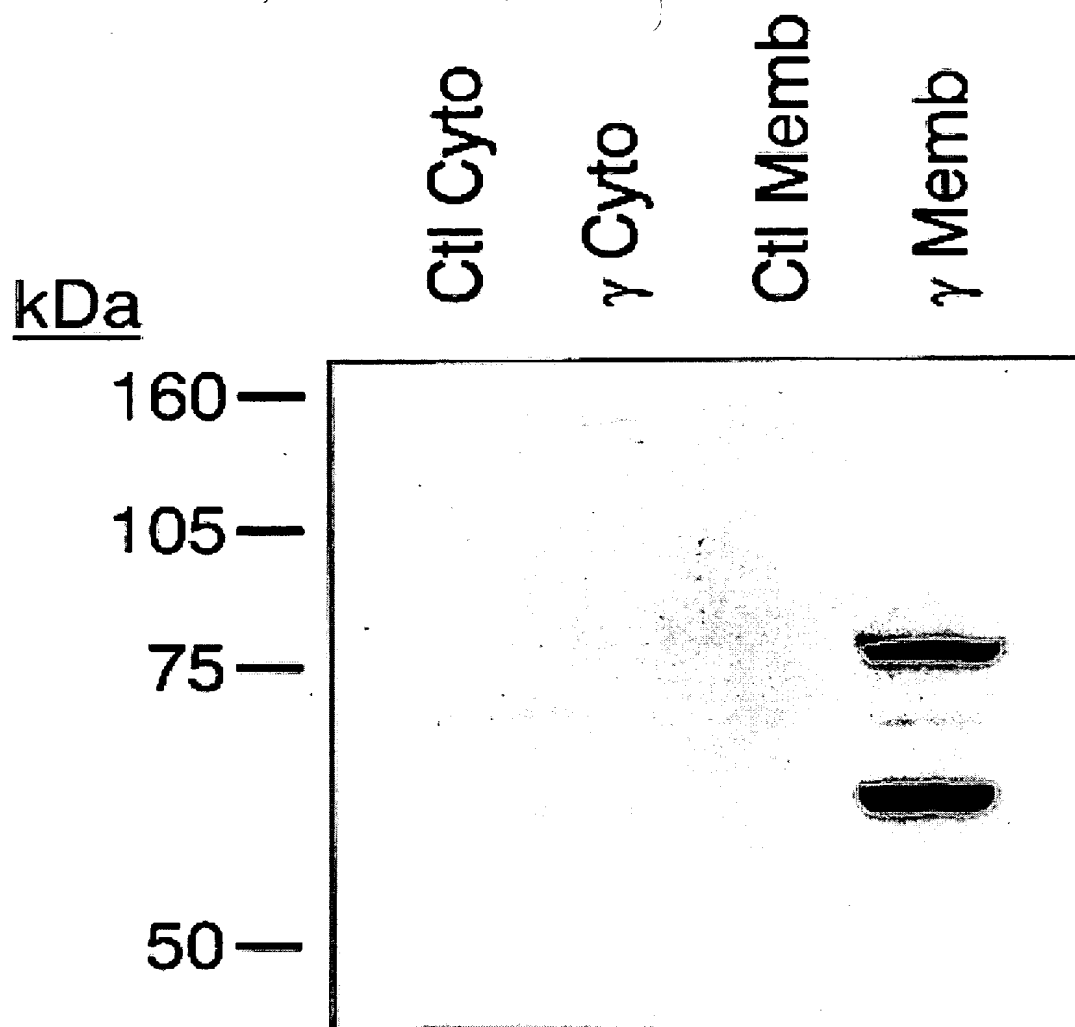


FIGURE 15

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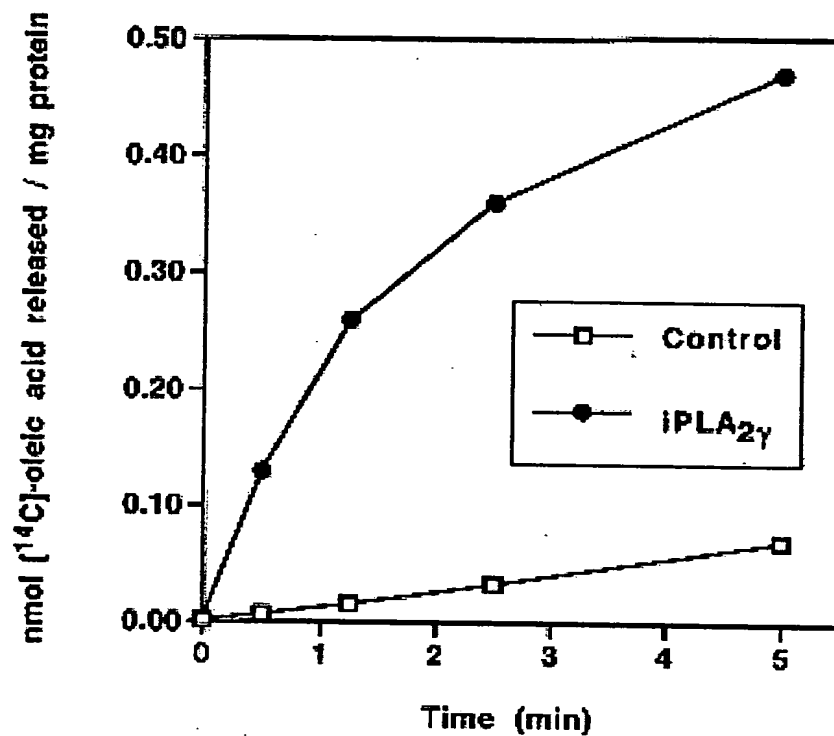


FIGURE 16

Title: CALCIUM INDEPENDENT PHOSPHOLIPASE A<sub>2</sub>γ  
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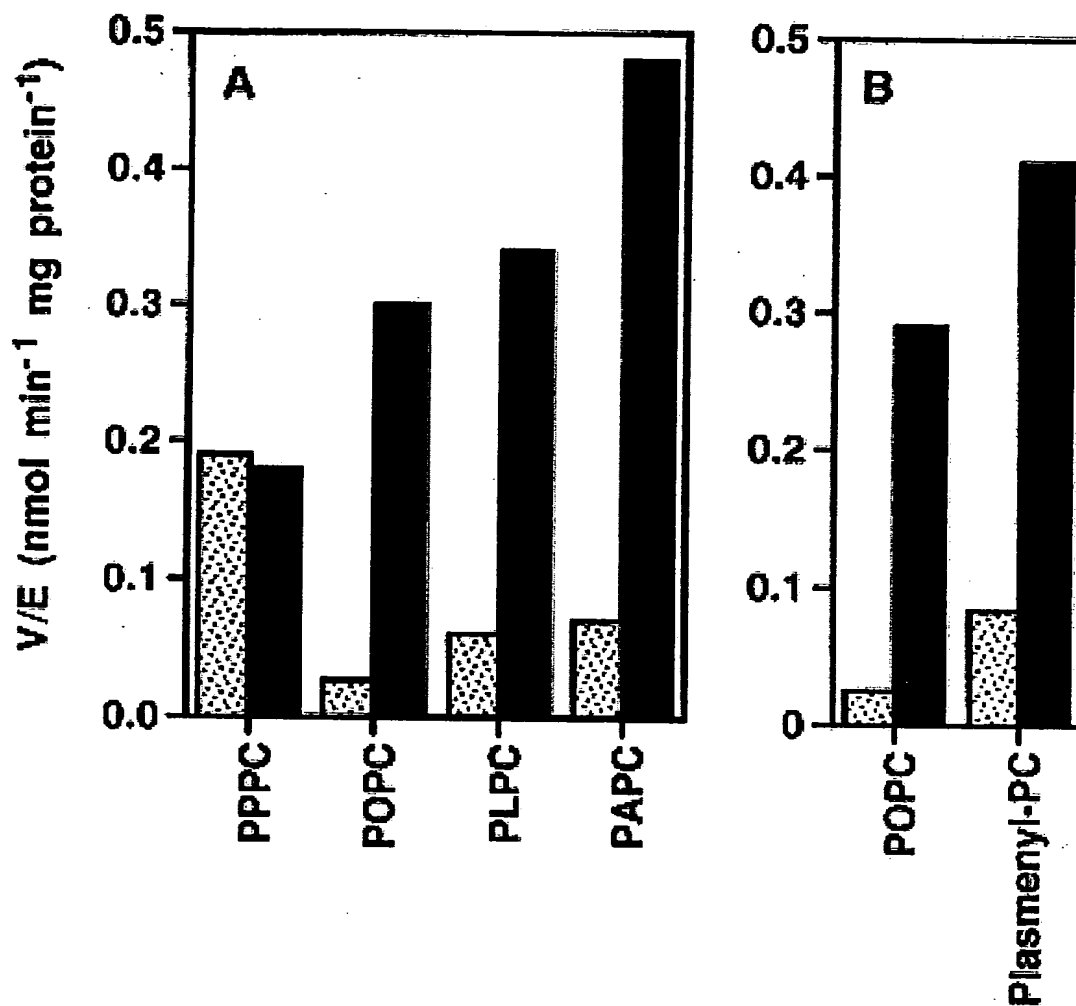


FIGURE 17

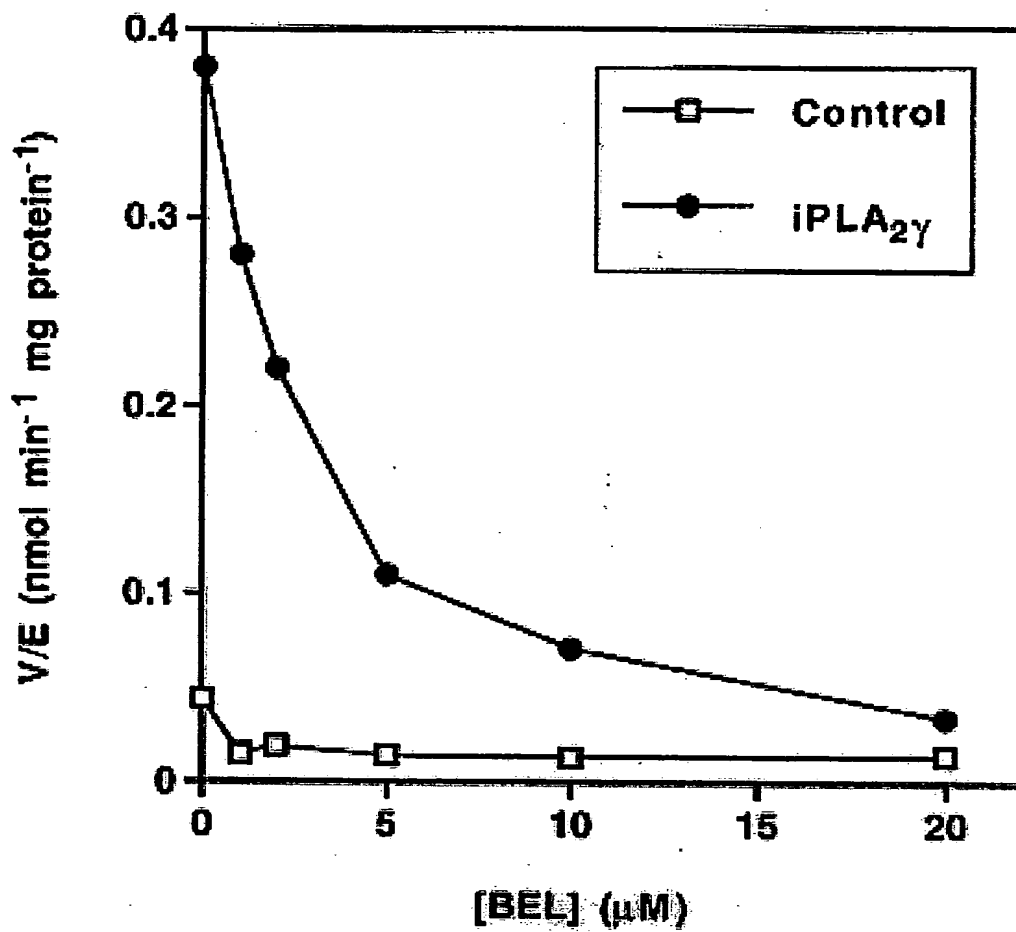
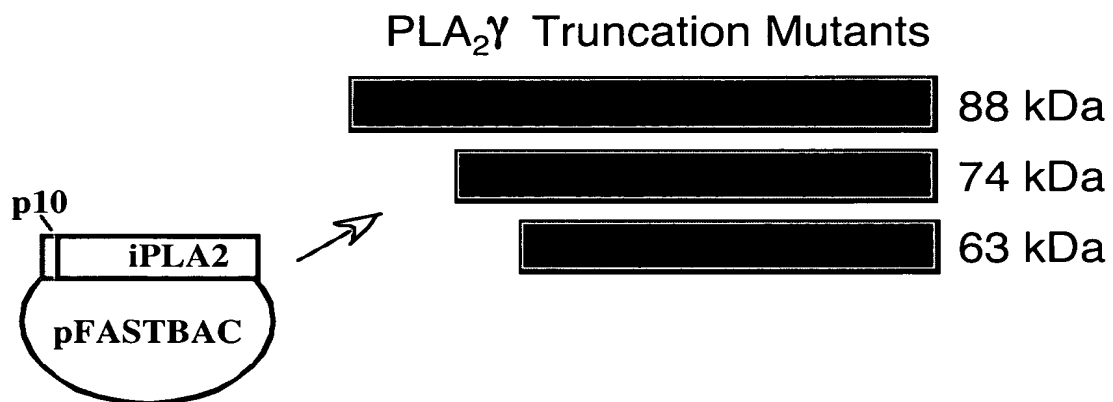
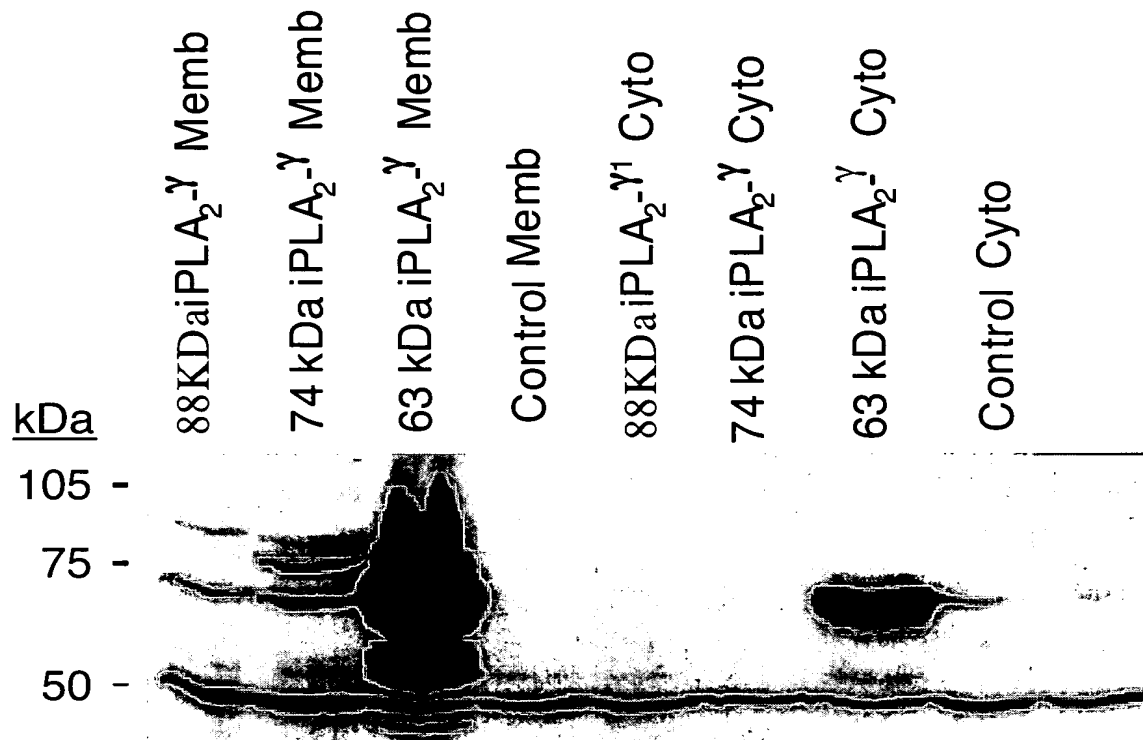


FIGURE 18

FIGURE 19

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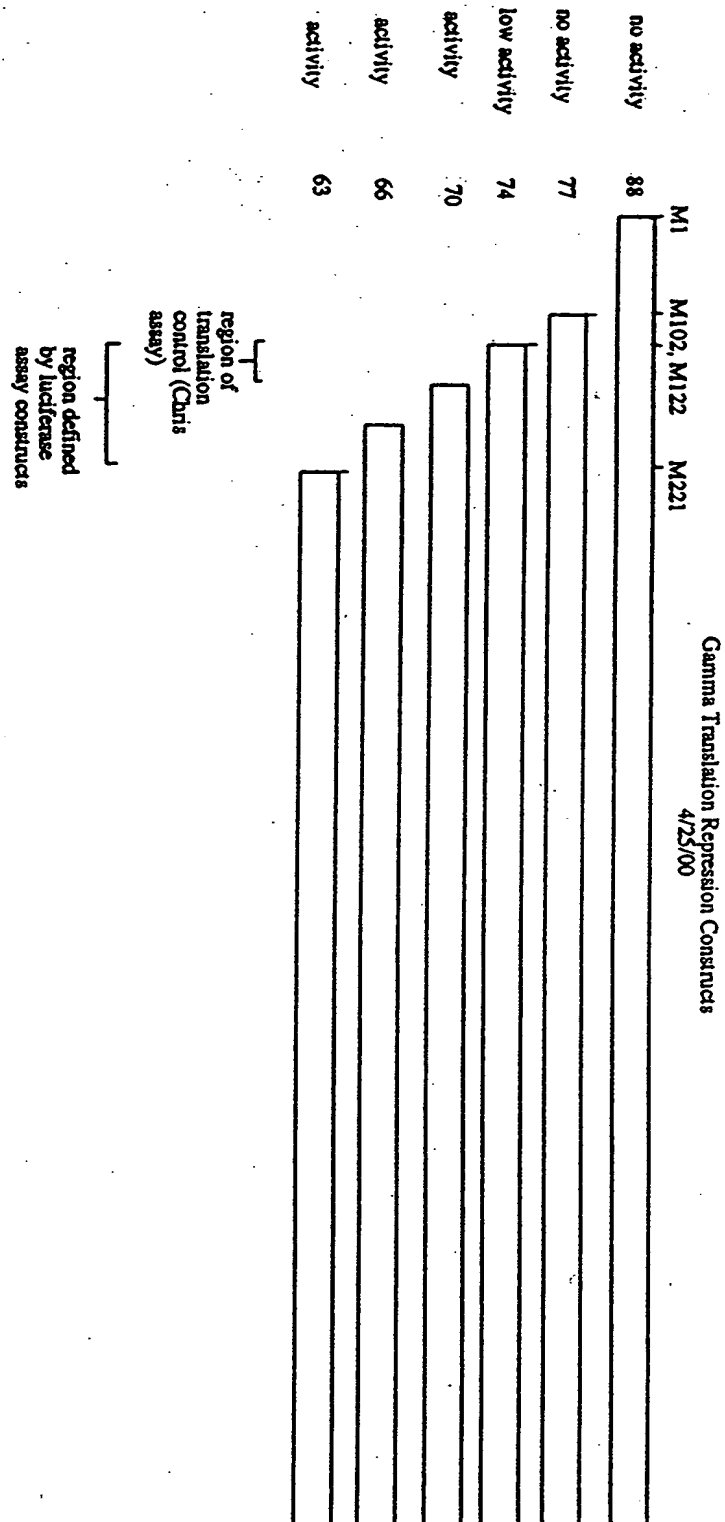
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FIGURE 20





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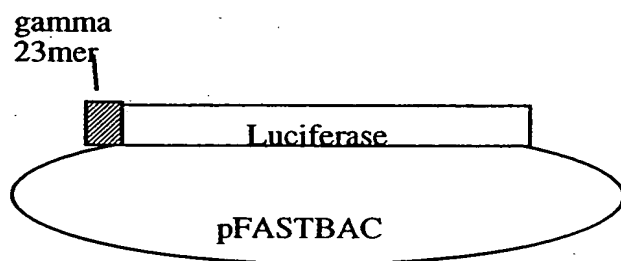
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FIGURE 21

Additionally, iPLA<sub>2</sub>γ sequences were inserted by ligation of 15-23mer annealed phosphorylated oligonucleotide pairs 5' of full-length luciferase coding sequence cloned into pFASTBAC via NotI/XbaI restrictions and then luciferase activity of recombinant protein produced in the Sf9 system was subsequently measured using the Luciferase Assay System of Promega.



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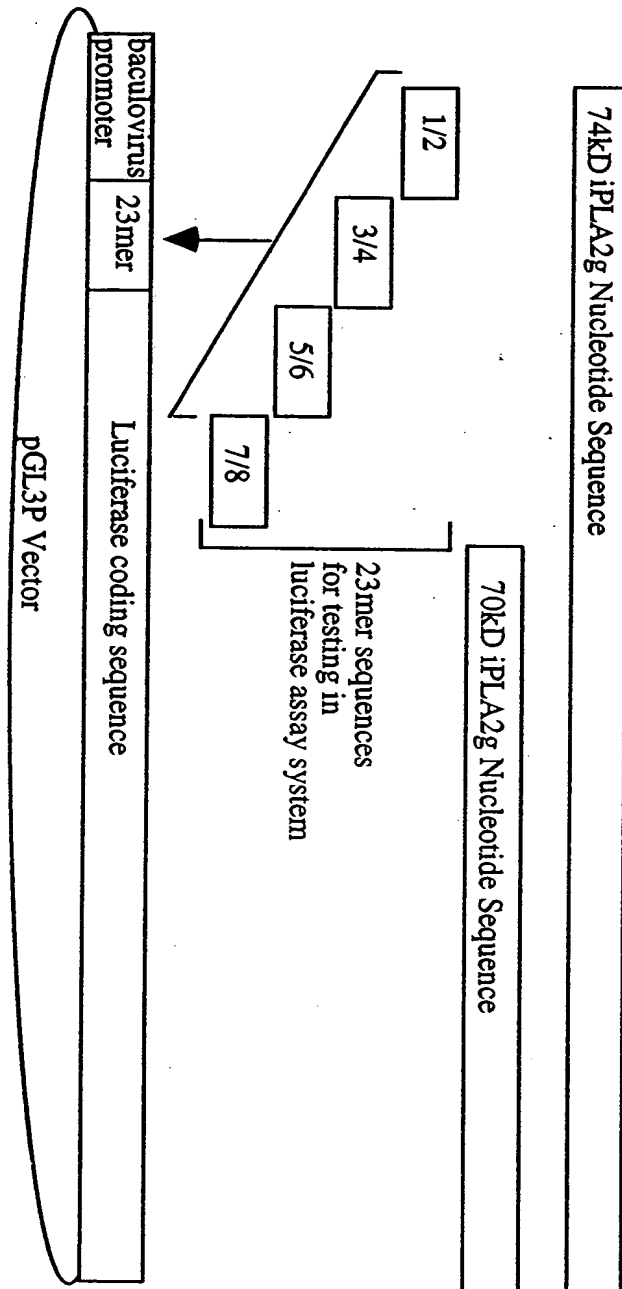
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FIGURE 22



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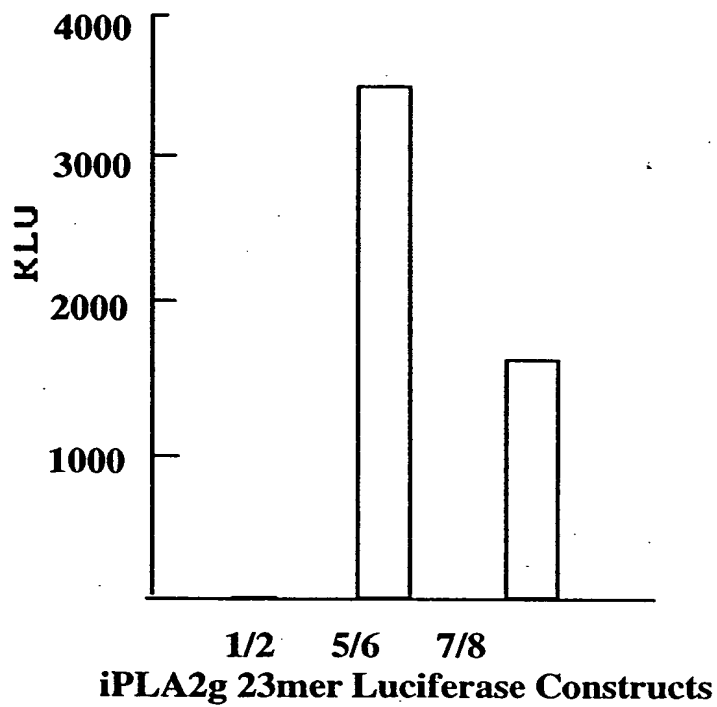
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**FIGURE 23. iPLA<sub>2</sub>γ Repressor Region**

**Phosphorylated oligo pairs  
for repression of iPLA<sub>2</sub>γ in the luciferase expression system:**

SEQ ID NO: 10	atgattccacgcttagctcaatttaagccaagtccccaattttaagaaagtcgtagtgctggttaaaacagaaaaacatcaaca
SEQ ID NO: 32	tcgacctgattccacgcttagctcaatt
SEQ ID NO: 36	ggactaaagtcgcaaatcgagtttaaccgg
SEQ ID NO: 33	
SEQ ID NO: 37	tcgactaagccaagtcaccaatttta gattcggttcaagggtttaaatccgg
SEQ ID NO: 34	
SEQ ID NO: 38	tcgacgaaaagtcgtagtgctgg gctttcatagcctatcacccgaccccg
SEQ ID NO: 35	
SEQ ID NO: 39	tcgacttaaacagaaaaacatcaaca gaatttgctctttgttagttgtccgg

**FIGURE 24**



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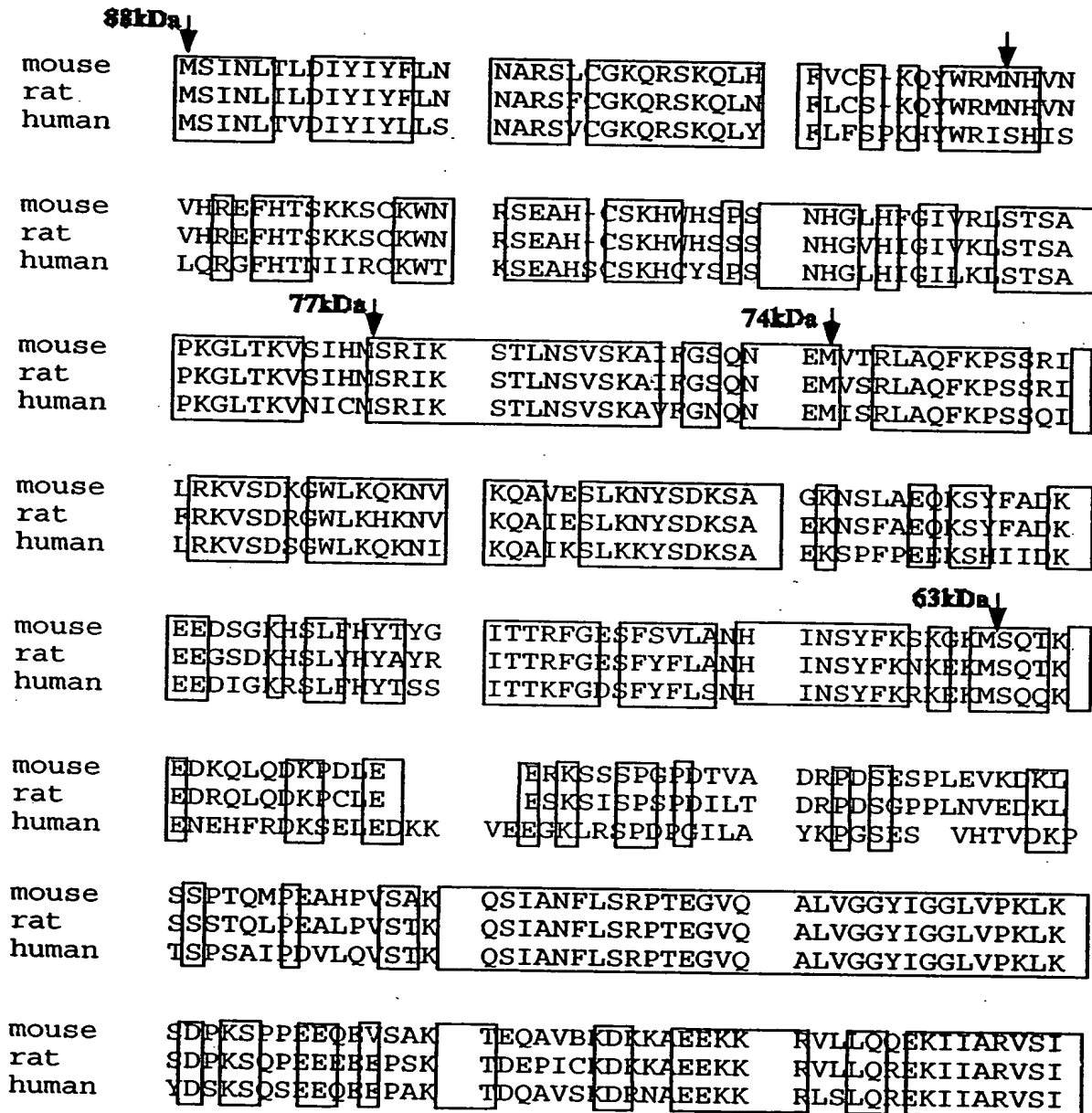
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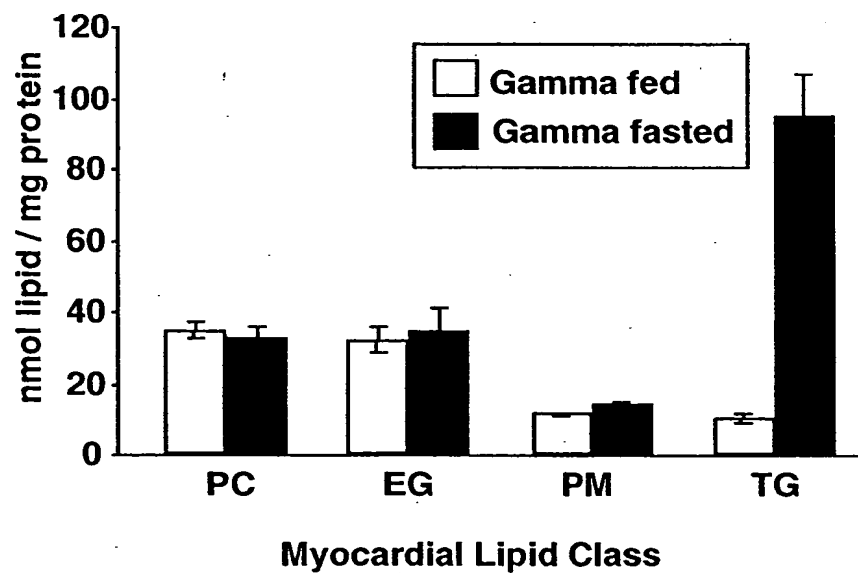
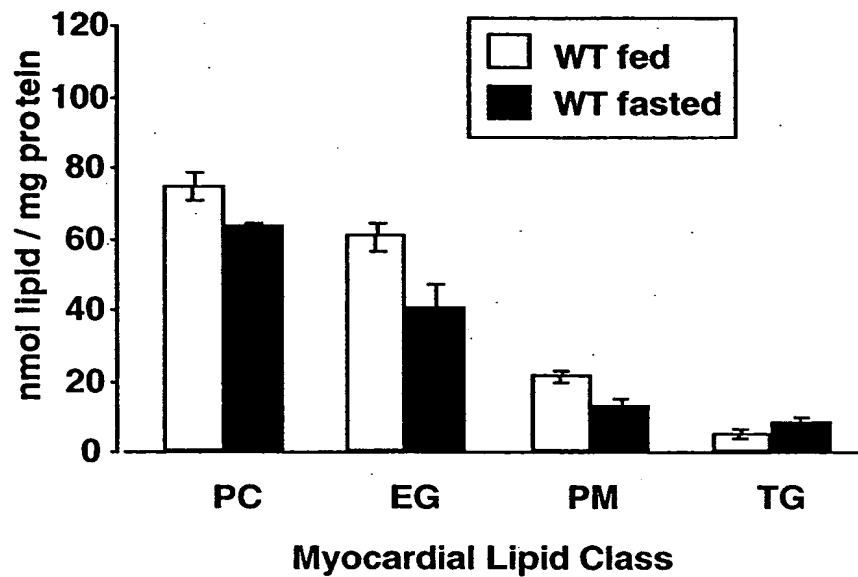
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**FIGURE 25**



SEQ ID NO: 40 = N terminal 353 amino acids of mouse iPLA<sub>2</sub> $\gamma$   
 SEQ ID NO: 41 = N terminal 353 amino acids of rat iPLA<sub>2</sub> $\gamma$   
 SEQ ID NO: 42 = N terminal 359 amino acids of human iPLA<sub>2</sub> $\gamma$

Fig. 26 Myocardial TAG Content of Fasted WT vs iPLA<sub>2</sub> $\gamma$  Transgenic Mice

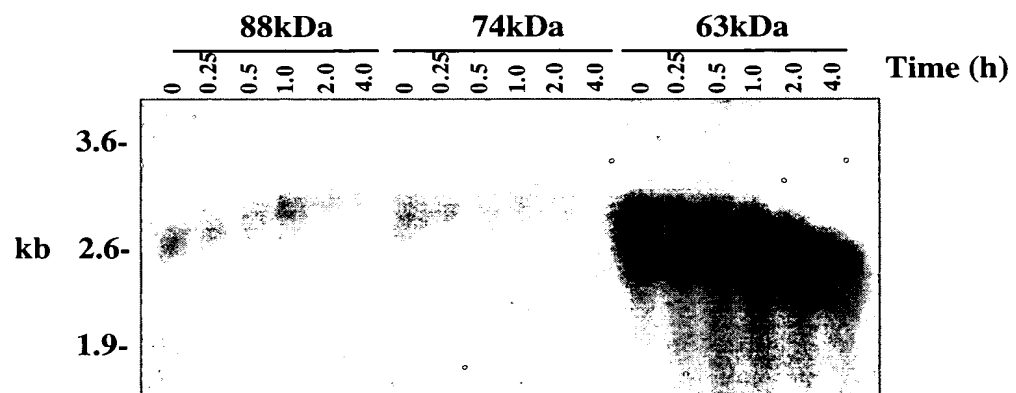


PC = Phosphatidylcholine  
EG= Ethanolamine Glycerophospholipids  
PM= PLasmalogen  
TG= Triacylglyceride

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**FIGURE 27**



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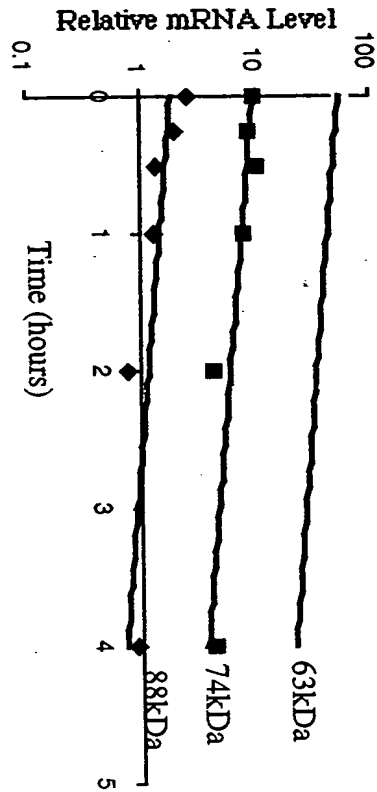


FIGURE 28. Quantitative PCR analysis of RNA stability of truncated iPLA<sub>2</sub> $\gamma$  S19 Expression



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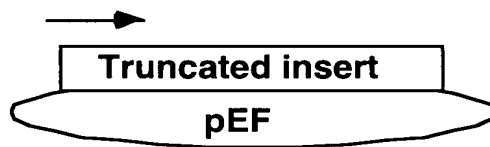
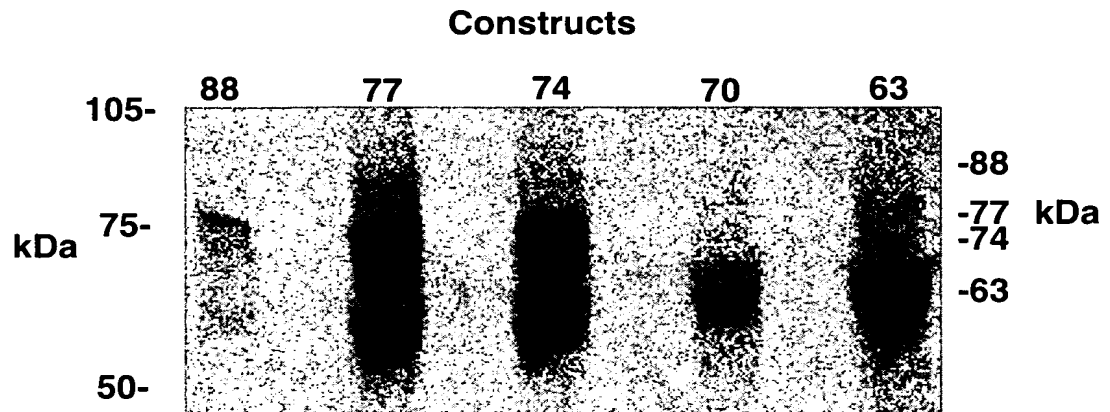
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FIGURE 29

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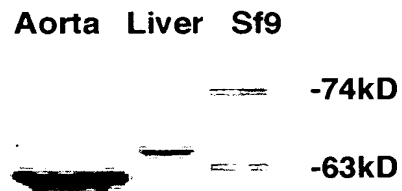


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**FIGURE 30**



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# iPLA<sub>2</sub> Gamma Functional Domains

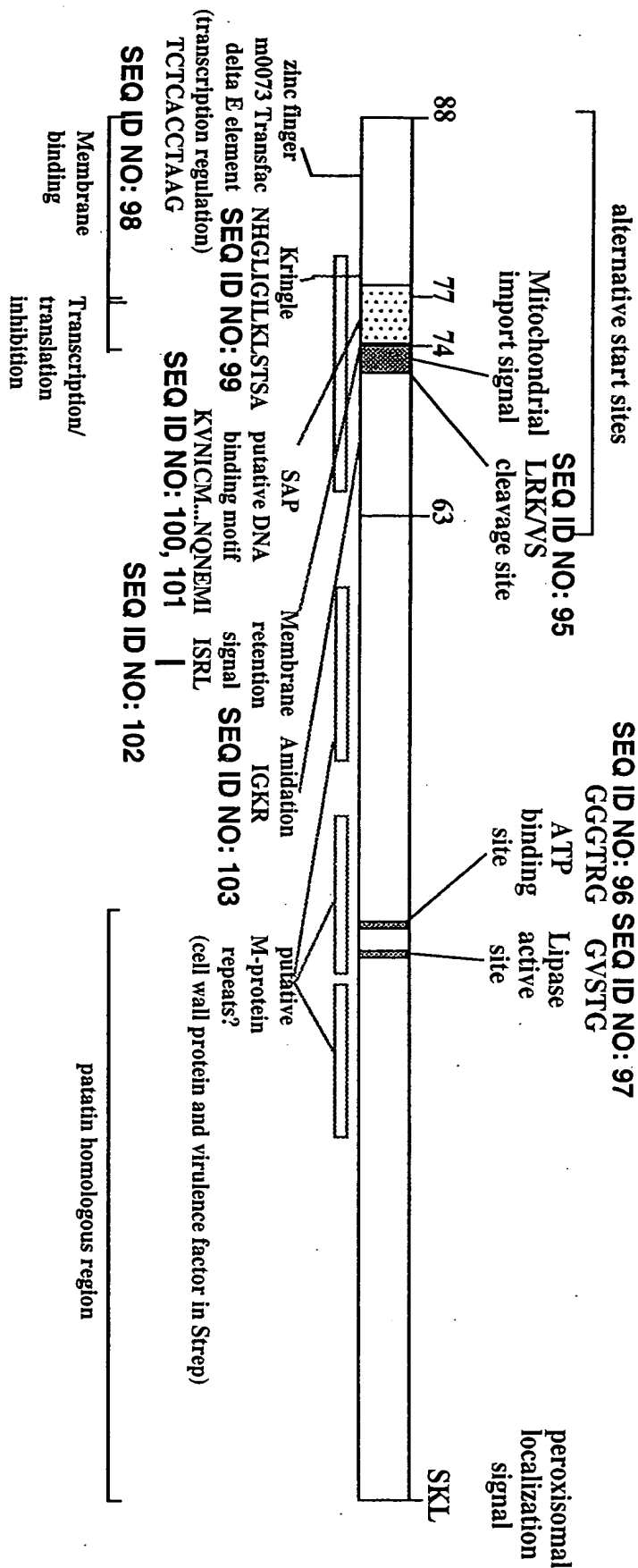


FIGURE 31

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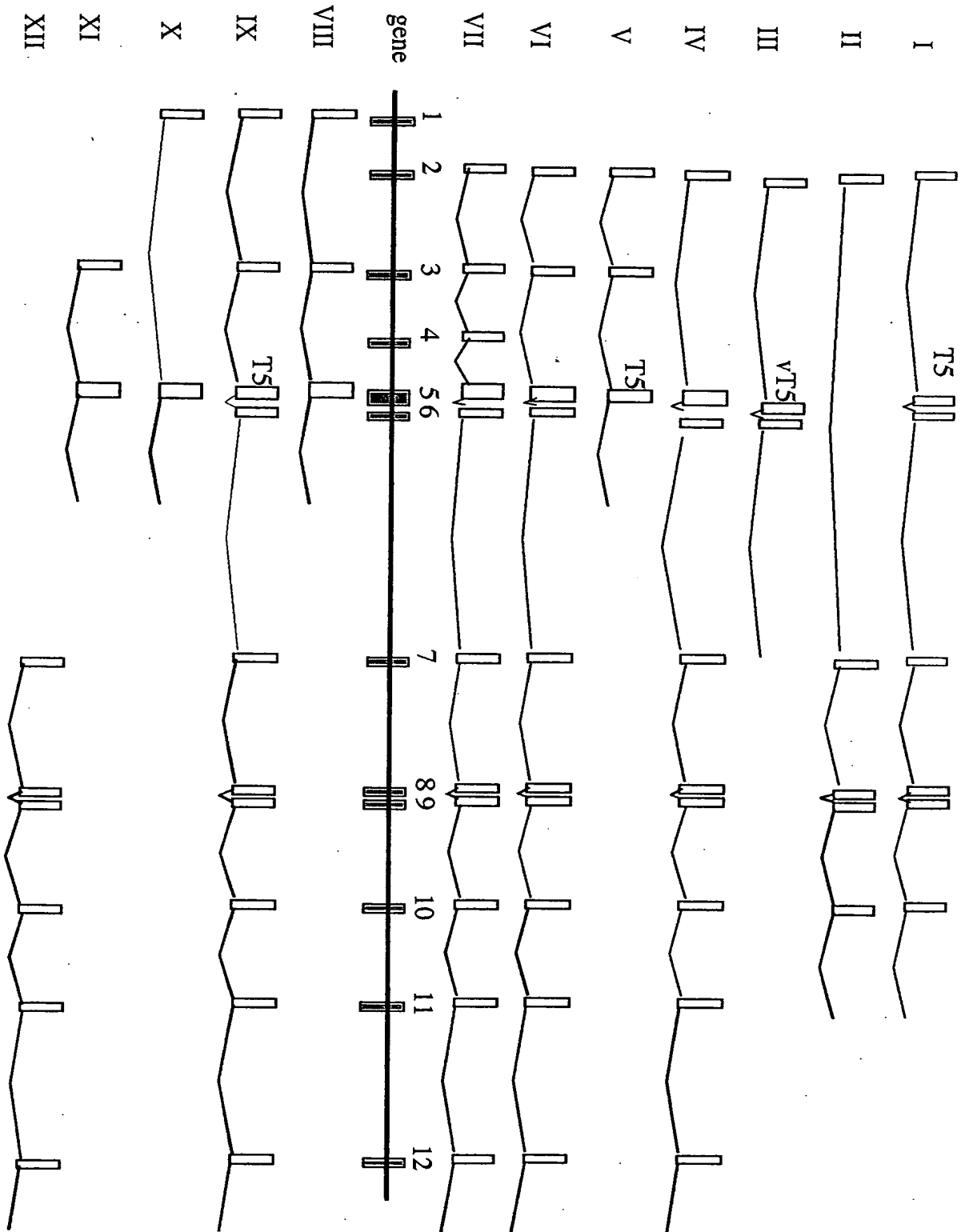


FIGURE 32

FIGURE 33

Promoter Analysis of iPLA<sub>2</sub> $\gamma$  Pre exon 2



**Conclusion:** sequence upstream of exon 2 has promoter activity. Enhancer activity resides in the region 200-400nt upstream of exon 2 (fragment IV). This region contains a CACG VNTR like sequence as well as sequences that match consensus sites for Sp1 (8), GATA1 (9), p300 (4), and Gcr1 (10). GC regions upstream (1) and downstream (7) of this positive promoter region commonly are negative regulatory elements. Truncated fragments (II and VI) each lacking a GC region have enhanced promoter activity while fragments (III and V) containing the GC regions but lacking region IV have minimal promoter activity. Presumably both GC regions are required for maximal inhibition. Region IV may have less than optimal promoter activity if positive promoter elements are immediately upstream or downstream of region IV.

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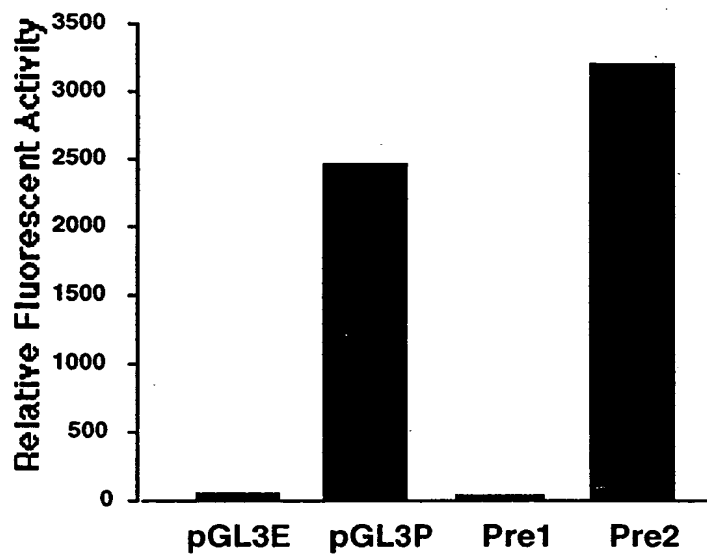
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**FIGURE 34. Promoter Activity of Pre Exon 1 and 2 Regions**



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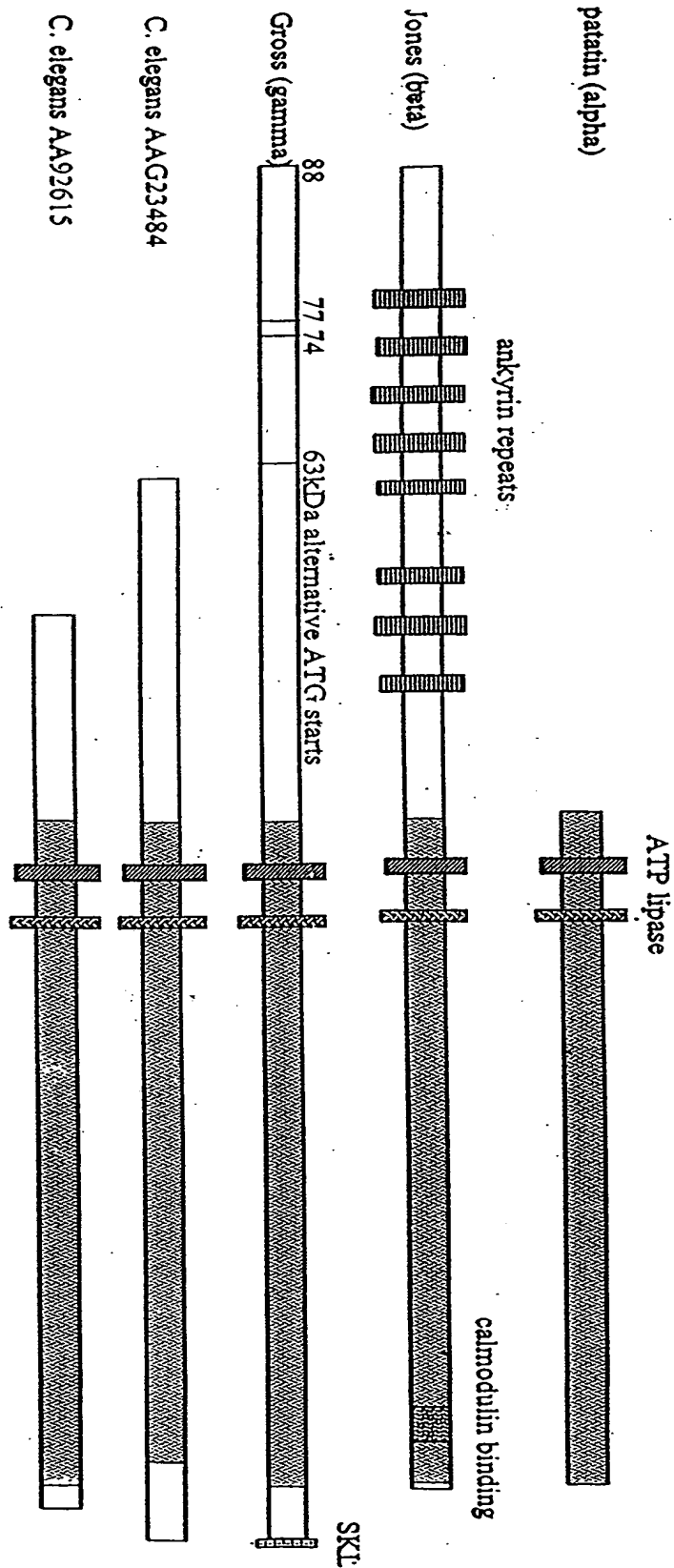
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FIGURE 35



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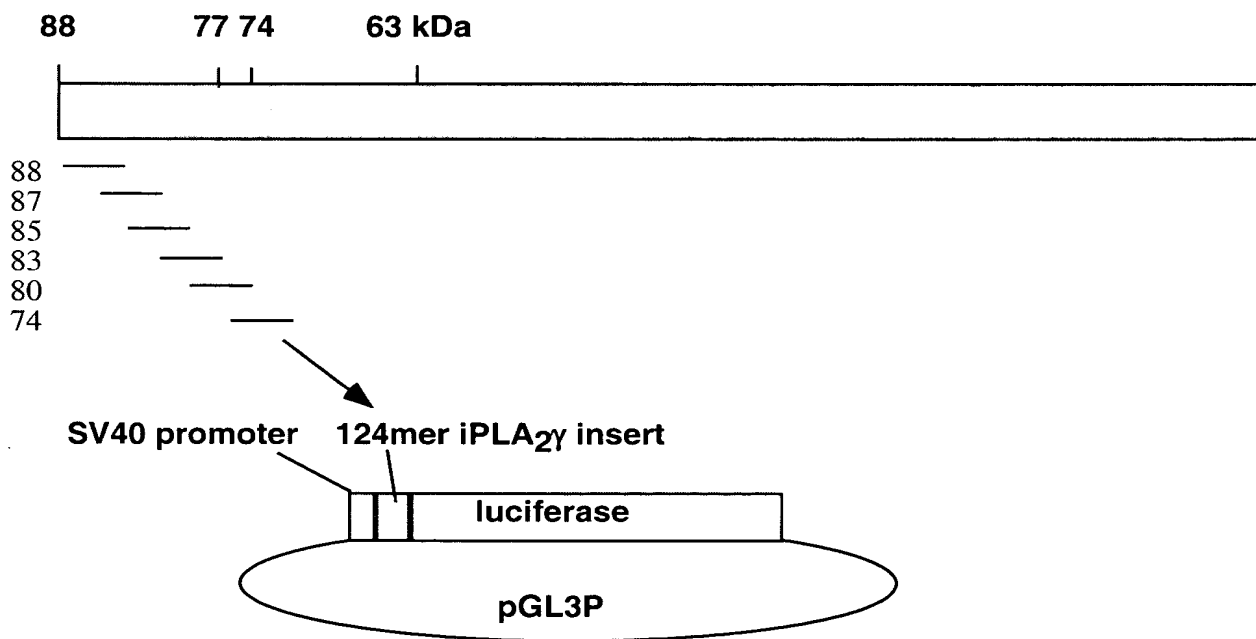
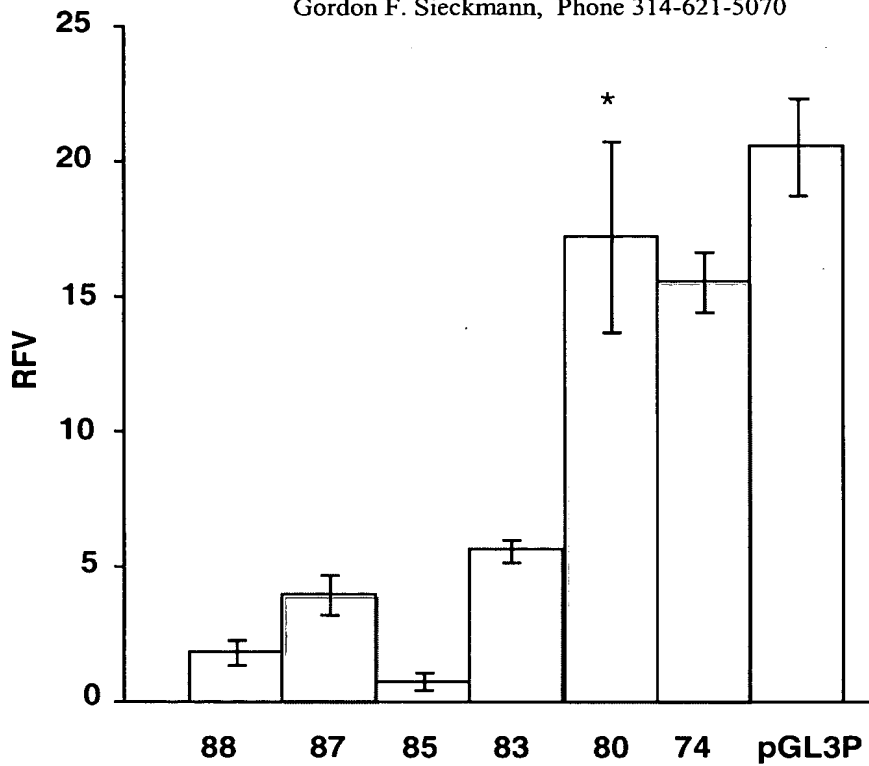


FIGURE 36



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FIGURE 37



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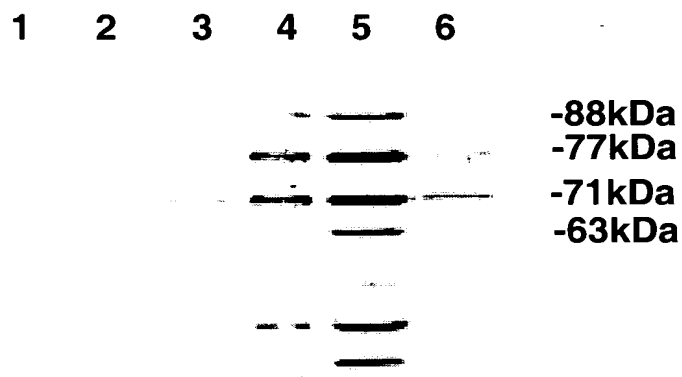


FIGURE 38

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FIGURE 39

Alignment of Mouse, Rat, and Human Pre-exon 2 Sequence

Mouse	3CGTCACTTCGCGCTGGGGGCGCGGGCGGTAGCGG-----TGGGTGTG--CTGGTCAC--3CCAGTGTTTGGGT	88
Rat	3CGTCACTTCGCGCTGGGGGCGCGGGCGGTAGCGG-----AGGTGAGG--CTG-TAGC--3CCAGTGTTTGGGT	89
Human	3CGTCACTTCGCGCTGGGGGCGCGAGCGGGGCGGGCTGAGTGGGTGCGACCTAGCTGCTGCGCCAGTGTTTGTGTT	90

Inr

SEQ ID NO:

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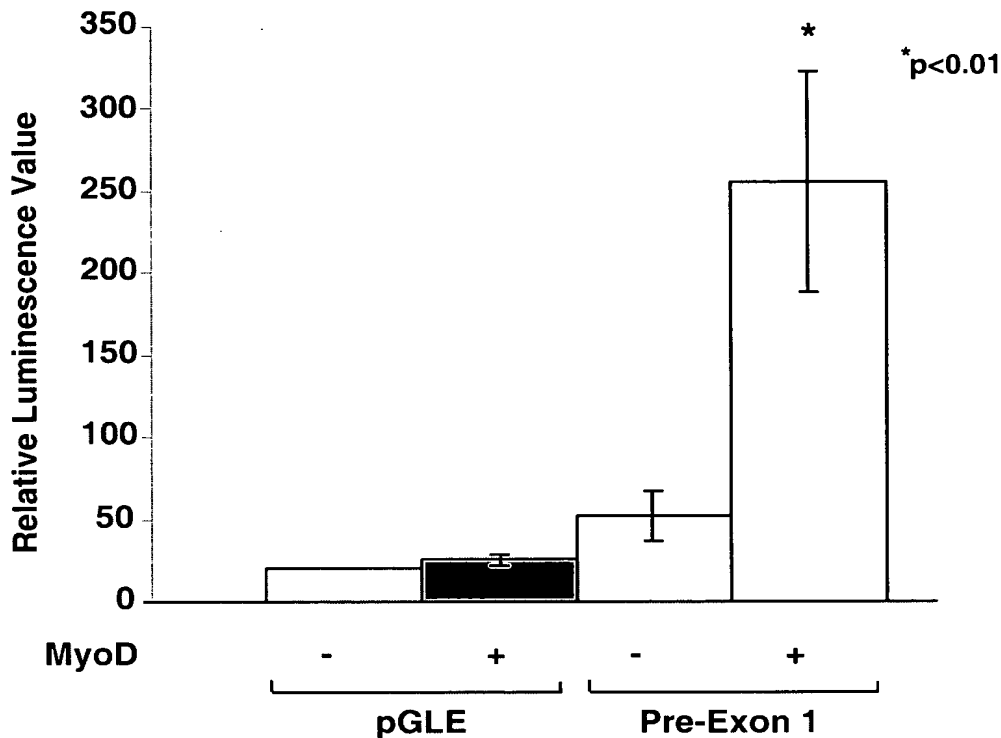
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FIGURE 40



FIGURE 41

# **MyoD Stimulation of Promoter Activity in Pre-Exon 1 Sequence of iPLA<sub>2</sub>γ**



## **Putative MyoD Elements within Pre-Exon 1 of iPLA<sub>2</sub>γ**

```

-395                                     -336
ATTATAATACTGTGTCAGCAACGGCAATAAGAGAAGTCAGCACAGGTGGAAGGAATGATTC
                                     GGACAGGTGGG
                                     E-box (MyoD)
-335                                     -138
ATTCTATGAGTAGTGAGGTAAGATTTTCCTGGCTGAAGGACAAACAAATCTTTAGGAGGA
-137                                     -77
CAAGGTGGAAGGGGAGCTAAGCCAACAGCATGACCAAGGCACTAAGTATGAAAAGCAACA
-75                                     -17
AGAGTATCTGGGGAAGTACAGGTGTGGCTGCAGGATAGAGAGTCAGAGGCAAGTGGTGAA
      CACAGGTGGTG                      CGACAGGTGGTG
      E-box (MyoD)                    E-box (MyoD)

-16      -1      1
AGTAAAGGCTGGAAGG TCAGCAGGGTCAGA
                        Exon 1
  
```

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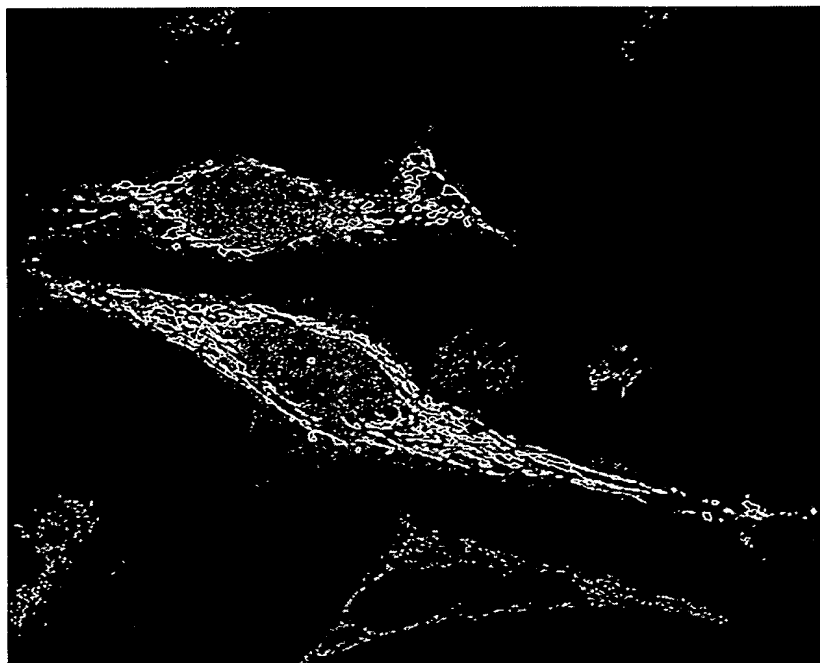
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**FIGURE 42A**



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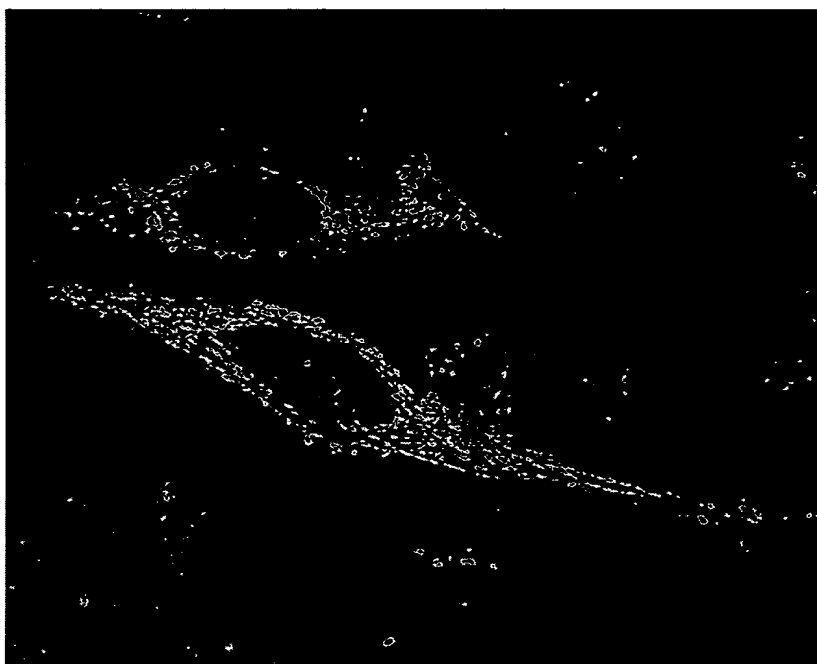
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**FIGURE 42B**



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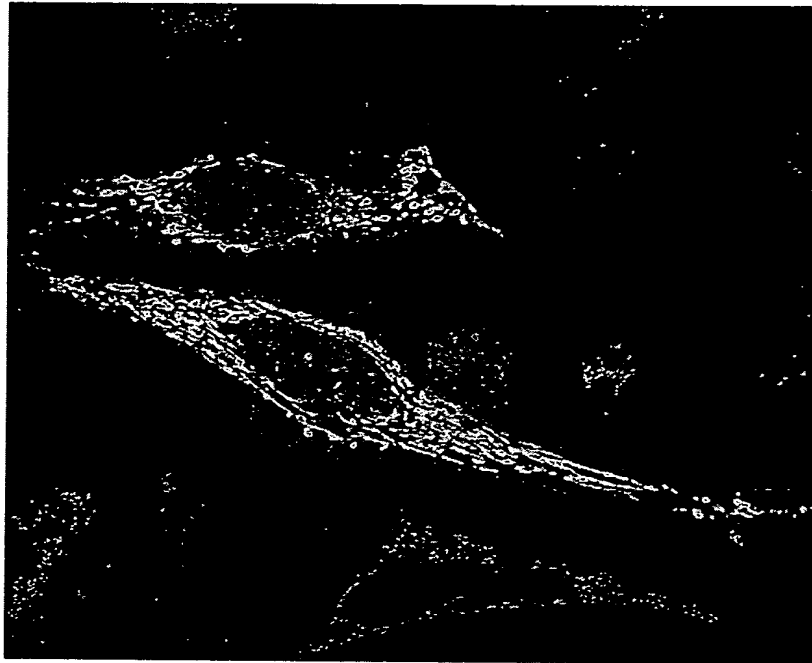
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**FIGURE 42C**





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Table I

Exon Number	Length (nt)	5' Intron Sequence	Corresponding AC005058 Residues	3' Intron Sequence
----------------	----------------	--------------------------	---------------------------------------	--------------------------

1 346 GGAAGG 135622-135327  
GTATGG  
SEQ ID NO: 29  
TCAGCAGGGTCAGAACCTATAATTTCATTCCGTATATTCT

GTGAAGATGTACAGCCAGCAAAAGCTTTTAAATTCGGGAA  
AACACGATTGGACTTGCACTTCAAAAAGATTACCGTGTT  
GCACAGAAGAGACTGACTGGGTCAGAGGTTAGTTACAGGC  
TGAAAAACCCAGTTTAGATGAAACTGAAGAGCAAGATGAA  
AGCCTGAACCTAGAGCAGTGAATGCCAATGTGAGCAGA  
GGAACGATTCAGAATAATTCTGCCGTAAACTCATCAGACT  
TCATGACTGATTAAAG

SEQ ID NO: 30

4 112 TCATAG 125571-125460  
GTAGGT  
TTTGGCCTTCTAGAGTGTTATACAGCTGGAATCATACTG

CTATGTCGGAATGTTGTGCTCTCAAAATTCATGTGA  
AATCATTAACCGCTAAAGTGATGTATTAAAG

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Table II  
iPLA<sub>2</sub>γ Splice Variants

Variant	Exons ESTs	Clone	Source
I	e2/TT5BI562455		testis
II	e2/T7 AL59775		unknown
III	e2/t5 BI333454	462	cervix heart
IV	e2/5 AF263947 BI596690; BI333453; BI553295 BG706376; BG708220 BG392963 AB041261	478	heart hippocampus hypothalamus testis T lymphocyte smooth muscle
V	e2/3/t5 BG699526; BG699526; BI550880 AL529506 R64045	507	hippocampus neuroblastoma smooth muscle
VI	e2/3/5 AA143503 BG502179 BG613307; BG701929; BG702929; BI547339 BG613307; BG719485; BG502179; BG771750 BG719485; BG613307	460.7	colon embryonal carcinoma hippocampus testis heart
VII	e2/3/4/5 BG723923	502	testis heart
VIII	e1/3/5 AV747051; AV747330		pituitary

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Table II (Continued)

Variant	Exons ESTs	Clone	Source
IX	e1/3/t5 AU136710; AK024335	492 467 485; 490	placenta HUVEC pancreas smooth muscle
X	e1/t5	494 466 460.1	smooth muscle myocardial pancreas
XI	e3/5	pan ap2/466.5	pancreatic

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Table III

<u>Construct Primer pairs 5' to 3' Sequence</u>		<u>SEQ ID NO:</u>
88	88f GTTGAAGCTTGTGTCTAATTAATCTGACTGTA	63
	88r TAGACCATGGTGGCTTATCCTCCAGTAATGC	64
87	87f GTGTAAAGCTTGAAGCAGAGAAGCAAGCAACTG	65
	87r ACTGCCATGGTGGCCTTCACTTTGGTCCATTAC	66
85	85f TGGAAAGCTTGGCCACATCAGTCTACAAG	67
	85r TGCTCCATGGTGGCATCCCAATATGTAAACCA	68
83	83f GAACCAAGCTTGAAGCAGACATCTTGCAGTAAGCA	69
	83r CAAAACATGTTGGCTACGGGACATACAAATGTTCA	70
80	80f GTTGAAGCTTTTGAAACTTAGCAGTCTGTC	71
	80r ATTCCATGGTGGCTGAATAATCATTTTCATTTTGATTGCC	72
74	74f TCAAAAGCTTATGAATTCACGTTAGCTC	73
	74r CTTTGCATGGTGGCTGTCACATAATTTTTC	74

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Table IV

Splice Variant	5' Exon Number	3' Exon Residues	5' Intron Sequence	3' Intron Sequence	5' Truncated Exon Sequence	SEQ ID NO:
X	1	GATTAAAG	gtatggtggt	acctccttag	TAATGCAAG	75, 76
III	2	GCATCCCG	gtaagtaggc	acctccttag	TAATGCAAG	91, 92

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Table V  
Sequence surrounding iPLA<sub>2</sub>γ ATG Start Sites

<u>Isoform</u> <u>NO.</u>	<u>Sequence</u>	<u>Matches to Kozak Consensus</u>	<u>SEO ID</u>
88kDa	T T T T A A G T T A T G T	1/12 adequate	79
77kDa	A A C A T T T G T A T G T	1/12 poor	80
74kDa	C A A A A T G A A A T G A	1/12 poor	81
63kDa	A A G G A A A A A A T G T	2/12 adequate	82
consensus	G C C G C C A C C A T G G		

G